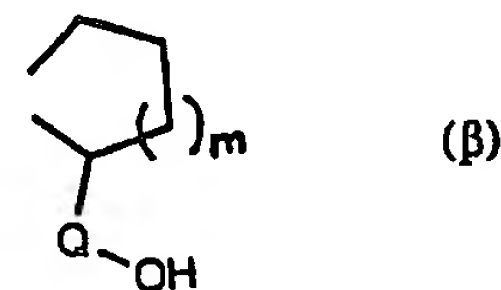
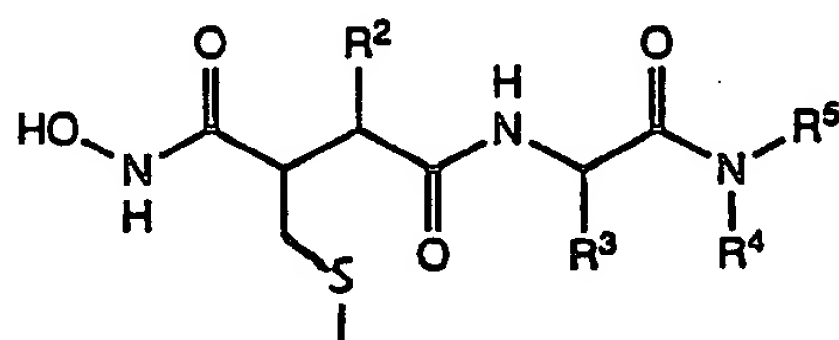
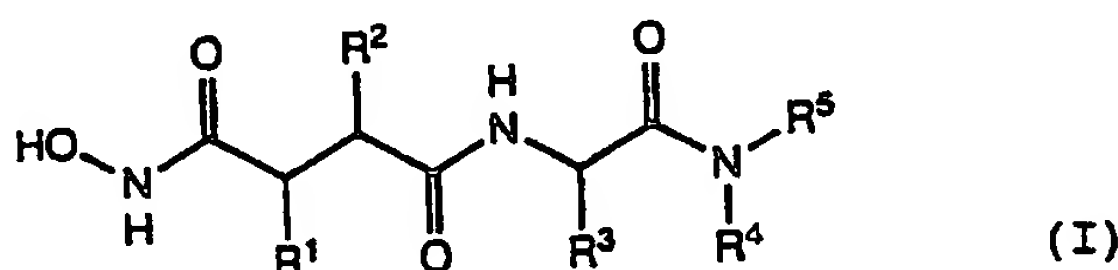




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(54) Title: HYDROXAMIC ACID BASED COLLAGENASE INHIBITORS**(57) Abstract**

Compounds of general formula (I) wherein R¹ represents a hydrogen atom or a C₁-C₆ alkyl, C₁-C₆ alkenyl, phenyl, phenyl(C₁-C₆)alkyl, C₁-C₆ alkylthiomethyl, phenylthiomethyl, substituted phenylthiomethyl, phenyl(C₁-C₆)alkylthiomethyl or heterocyclylthiomethyl group; or R¹ represents -S-R^x wherein R^x represents a group α; R² represents a hydrogen atom or a C₁-C₆ alkyl, C₁-C₆ alkenyl, phenyl(C₁-C₆)alkyl, cycloalkyl(C₁-C₆)alkyl, or cycloalkenyl(C₁-C₆)alkyl; R³ represents an amino acid side chain or a C₁-C₆ alkyl, benzyl, (C₁-C₆)alkoxybenzyl, benzyloxy(C₁-C₆)alkyl or benzyloxybenzyl group; R⁴ represents a hydrogen atom or a methyl group; R⁵ represents a group (CH₂)_nA; or R⁴ and R⁵ together represent a group β; Q represents CH₂ or CO; m is an integer from 1 to 3; n is an integer from 1 to 6; and A represents a hydroxy, (C₁-C₆)alkoxy, (C₂-C₇)acyloxy, (C₁-C₆)alkylthio, phenylthio, (C₂-C₇)acylamino or N-pyrrolidone group or a salt and/or N-oxide and/or useful in the management of disease involving tissue degradation and/or the promotion of wound healing. Diseases involving tissue degradation include arthropathy (particularly rheumatoid arthritis), inflammation, dermatological diseases, bone resorption diseases and tumour invasion.

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Hydroxamic acid based collagenase inhibitors

COMPOUNDS

This invention relates to pharmaceutically and veterinarily active compounds, which are derivatives of hydroxamic acid.

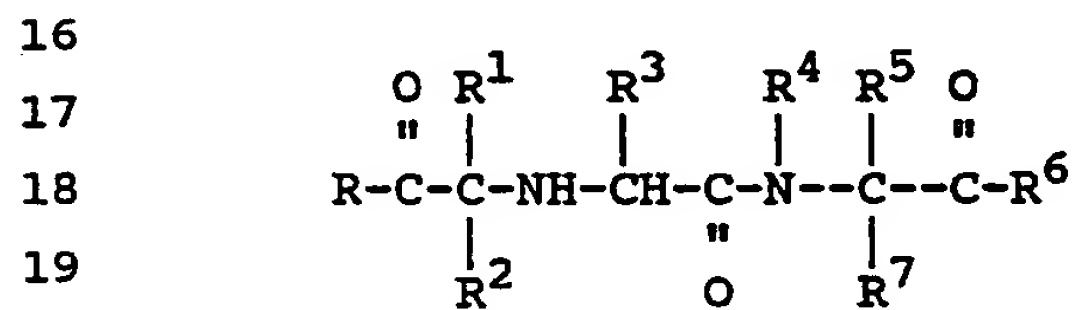
The compounds of the present invention act as inhibitors of metalloproteases involved in tissue degradation, such as collagenase, which initiates collagen breakdown, stromelysin (proteoglycanase), gelatinase and collagenase (IV). There is evidence implicating collagenase as one of the key enzymes in the breakdown of articular cartilage and bone in rheumatoid arthritis (Arthritis and Rheumatism, 20, 1231 - 1239, 1977). Potent inhibitors of collagenase and other metalloproteases involved in tissue degradation are useful in the treatment of rheumatoid arthritis and related diseases in which collagenolytic activity is important. Inhibitors of metalloproteases of this type can therefore be used in treating or preventing conditions which involve tissue breakdown; they are therefore useful in the treatment of arthropathy, dermatological conditions, bone resorption, inflammatory diseases and tumour invasion and in the promotion of wound healing. Specifically, compounds of the present invention may be useful in the treatment of osteopenias such as osteoporosis, rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration and tumour invasion.

A number of small peptide like compounds which inhibit metalloproteases have been described. Perhaps the most notable of these are those relating to the

1 angiotensin converting enzyme (ACE) where such
 2 agents act to block the conversion of the decapeptide
 3 angiotensin I to angiotensin II a potent pressor
 4 substance. Compounds of this type are described in
 5 EP-A-0012401.

6
 7 Certain hydroxamic acids have been suggested as
 8 collagenase inhibitors as in US-A-4599361 and
 9 EP-A-0236872. Other hydroxamic acids have been prepared
 10 as ACE inhibitors, for example in US-A-4105789, while
 11 still others have been described as enkephalinase
 12 inhibitors as in US-A-4496540.

13
 14 EP-A-0012401 discloses antihypertensive compounds of
 15 the formula:



18
 19
 20
 21 wherein

22
 23 R and R⁶ are the same or different and are hydroxy,
 24 alkoxy, alkenoxy, dialkylamino alkoxy, acylamino
 25 alkoxy, acyloxy alkoxy, aryloxy, alkyloxy, substituted
 26 aryloxy or substituted aralkoxy wherein the substituent
 27 is methyl, halo, or methoxy, amino, alkylamino,
 28 dialkylamino, aralkylamino or hydroxyamino;

29
 30 R¹ is hydrogen, alkyl of from 1 to 20 carbon atoms,
 31 including branched, cyclic and unsaturated alkyl
 32 groups;

33

1 substituted alkyl wherein the substituent is halo,
2 hydroxy, alkoxy, aryloxy amino, alkylamino,
3 dialkylamino, acrylamino, arylamino, guanidino,
4 imidazolyl, indolyl, mercapto, alkylthio, arylthio,
5 carboxy, carboxamido, carbalkoxy, phenyl, substituted
6 phenyl wherein the substituent is alkyl, alkoxy or
7 halo; aralkyl or heteroaralkyl, aralkenyl or
8 heteroaralkenyl, substituted aralkyl, substituted
9 heteroaralkyl, substituted aralkenyl or substituted
10 heteroaralkenyl, wherein the substituent is halor or
11 dihalo, alkyl, hydroxy, alkoxy, amino, aminomethyl,
12 acrylamino, dialkylamino, alkylamino, carboxyl,
13 haloalkyl, cyano or sulphonamido, aralkyl or
14 heteroaralkyl substituted on the alkyl portion by
15 amino or acylamino;

16
17 R^2 and R^7 are hydrogen or alkyl;
18

19 R^3 is hydrogen, alkyl, phenylalkyl,
20 aminomethylphenylalkyl, hydroxyphenylalkyl,
21 hydroxyalkyl, acetylaminoalkyl, acylaminoalkyl,
22 acylaminoalkyl aminoalkyl, dimethylaminoalkyl,
23 haloalkyl, guanidinoalkyl, imidazolylalkyl,
24 indolylalkyl, mercaptoalkyl and alkylthioalkyl;

25
26 R^4 is hydrogen or alkyl;
27

28 R^5 is hydrogen, alkyl, phenyl, phenylalkyl,
29 hydroxyphenylalkyl, hydroxyalkyl, aminoalkyl,
30 guanidinoalkyl, imidazolylalkyl, indolylalkyl,
31 mercaptoalkyl or alkylthioalkyl;

32

33

1 R⁴ and R⁵ may be connected together to form an alkylene
 2 bridge of from 2 to 4 carbon atoms, an alkylene bridge
 3 of from 2 to 3 carbon atoms and one sulphur atom, an
 4 alkylene bridge of from 3 to 4 carbon atoms containing
 5 a double bond or an alkylene bridge as above,
 6 substituted with hydroxy, alkoxy or alkyl and the
 7 pharmaceutically acceptable salts thereof.

8

9 US-A-4599361 discloses compounds of the formula:

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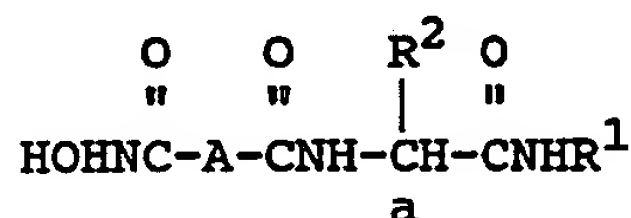
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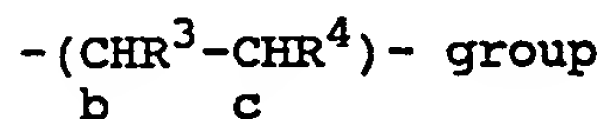
wherein

R¹ is C₁-C₆ alkyl;

R² is C₁-C₆ alkyl, benzyl, benzyloxybenzyl, (C₁-C₆ alkoxy)benzyl or benzyloxy(C₁-C₆ alkyl);

a is a chiral centre with optional R or S stereochemistry;

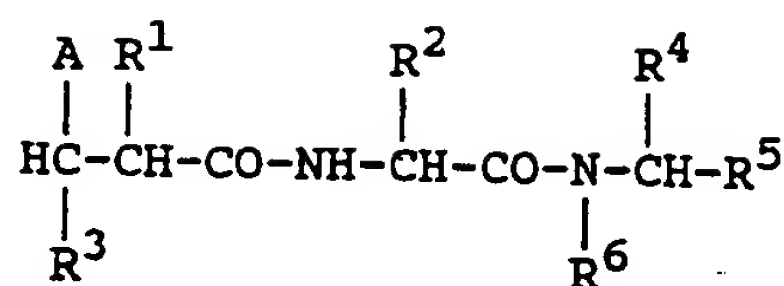
A is a



or a -(CR³=CR⁴)- group wherein b and c are chiral centres with optional R or S stereochemistry;

R³ is hydrogen, C₁-C₆ alkyl, phenyl or phenyl(C₁-C₆ alkyl) and R⁴ is hydrogen, C₁-C₆ alkyl, phenyl(C₁-C₆ alkyl), cycloalkyl or cycloalkyl(C₁-C₆ alkyl).

EP-A-0236872 discloses generically compounds of the formula



wherein

A represents a group of the formula $HN(OH)-CO-$ or $HCO-N(OH)-$;

R^1 represents a C_2-C_5 alkyl group;

R^2 represents the characterising group of a natural alpha-amino acid in which the functional group can be protected, amino groups may be acylated and carboxyl groups can be amidated, with the proviso that R^2 can not represent hydrogen or a methyl group;

R^3 represents hydrogen or an amino, hydroxy, mercapto, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acylamino, C_1-C_6 -alkylthio, aryl- $(C_1-C_6$ alkyl)-, amino- $(C_1-C_6$ -alkyl)-, hydroxy $(C_1-C_6$ -alkyl)-, mercapto $(C_1-C_6$ alkyl) or carboxy $(C_1-C_6$ alkyl) group, wherein the amino, hydroxy, mercapto or carboxyl groups can be protected and the amino groups may be acylated or the carboxyl groups may be amidated;

R^4 represents hydrogen or a methyl group;

1 R⁵ represents hydrogen or a C₁-C₆ acyl, C₁-C₆
 2 alkoxy-C₁-C₆ alkyl, di(C₁-C₆-alkoxy)methylene, carboxy,
 3 (C₁-C₆ alkyl)carbiny, (C₁-C₆ alkoxy)carbiny,
 4 arylmethoxy carbiny, (C₁-C₆ alkyl)amino carbiny or
 5 arylamino carbiny group; and

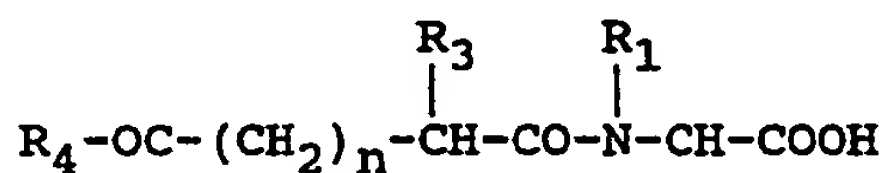
6
 7 R⁶ represents hydroxy or a methylene group; or

8
 9 R² and R⁴ together represent a group-(CH₂)_n-, wherein n
 10 represents a number from 4 to 11; or

11
 12 R⁴ and R⁵ together represent a trimethylene group;

13
 14 and pharmaceutically acceptable salts of such
 15 compounds, which are acid or basic.

16
 17 US-A-4105789 generically discloses compounds which have
 18 the general formula



22
 23 and salts thereof, wherein

24
 25 R₁ is hydrogen, lower alkyl, phenyl lower alkylene,
 26 hydroxy-lower alkylene, hydroxyphenyl lower
 27 alkylene, amino-lower alkylene, guanidine lower
 28 alkylene, mercapto-lower alkylene, lower
 29 alkyl-mercapto-lower alkylene, imidazolyl lower
 30 alkylene, indolyl-lower alkylene or carbamoyl
 31 lower alkylene;

32 R₂ is hydrogen or lower alkyl;

33 R₃ is lower alkyl or phenyl lower alkylene;

1 R_4 is hydroxy, lower alkoxy or hydroxyamino; and
2 n is 1 or 2.

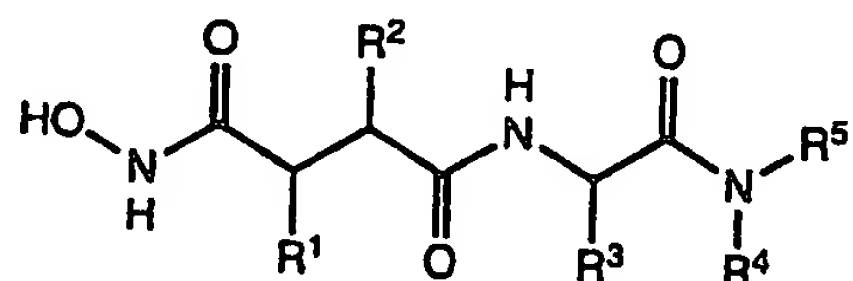
3
4 US-A-4496540 discloses compounds of the general
5 formula:

6
7 A-B-NHOH
8

9 wherein A is one of the aromatic group-containing amino
10 acid residues L-tryptophyl, D-tryptophyl, L-tyrosyl,
11 D-tyrosyl, L-phenylalanyl, or D-phenylalanyl, and B is
12 one of the amino acids glycine, L-alanine, D-alanine,
13 L-leucine, D-leucine, L-isoleucine, or D-isoleucine;
14 and pharmaceutically acceptable salts thereof.

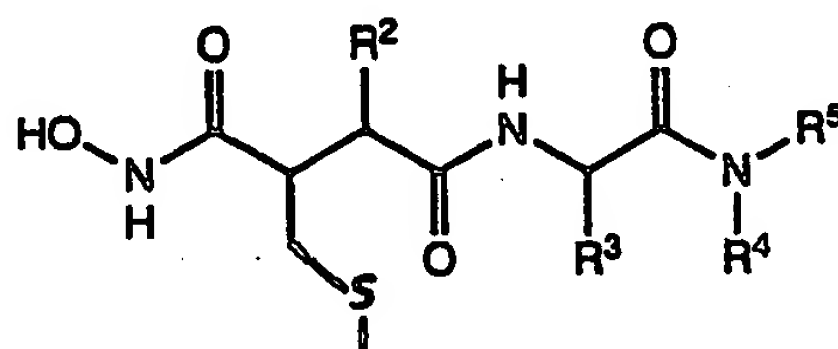
15
16 It would be desirable to improve on the solubility of
17 known collagenase inhibitors and/or stromelysin
18 inhibitors (whether as the free base or the salt) and,
19 furthermore, increases in activity have also been
20 sought. It is not a simple matter, however, to predict
21 what variations in known compounds would be desirable
22 to increase or even retain activity; certain
23 modifications of known hydroxamic acid derivatives have
24 been found to lead to loss of activity.

25
26 According to a first aspect of the invention, there is
27 provided a compound of general formula I:



wherein:

R^1 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6 alkenyl, phenyl, phenyl(C_1-C_6)alkyl, C_1-C_6 alkylthiomethyl, phenylthiomethyl, substituted phenylthiomethyl, phenyl(C_1-C_6)alkylthiomethyl or heterocyclylthiomethyl group; or R^1 represents $-S-R^x$ wherein R^x represents a group



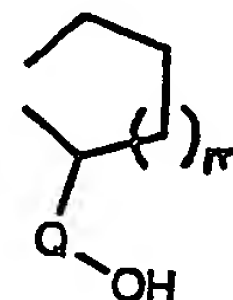
R^2 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6 alkenyl, phenyl(C_1-C_6)alkyl, cycloalkyl(C_1-C_6)alkyl, or cycloalkenyl(C_1-C_6)alkyl;

R^3 represents an amino acid side chain or a C_1-C_6 alkyl, benzyl, (C_1-C_6)alkoxybenzyl, benzyloxy- (C_1-C_6)alkyl or benzyloxybenzyl group;

R^4 represents a hydrogen atom or a methyl group;

R^5 represents a group $(CH_2)_nA$;

or R^4 and R^5 together represent a group



1 Q represents CH_2 or CO;

2

3 m is an integer from 1 to 3;

4

5 n is an integer from 1 to 6; and

6

7 A represents a hydroxy, (C_1-C_6) alkoxy,
8 (C_2-C_7) acyloxy, (C_1-C_6) alkylthio, phenylthio,
9 (C_2-C_7) acylamino or N-pyrrolidone group

10

11 or a salt and/or N-oxide and/or (where the compound is
12 a thio-compound) a sulphoxide or sulphone thereof.

13

14 Hereafter in this specification, the term "compound"
15 includes "salt" unless the context requires otherwise.

16

17 As used herein the term " C_1-C_6 alkyl" refers to a
18 straight or branched chain alkyl moiety having from
19 one to six carbon atoms, including for example,
20 methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl,
21 pentyl and hexyl, and cognate terms (such as " C_1-C_6
22 alkoxy") are to be construed accordingly.

23

24 The term " C_1-C_6 alkenyl" refers to a straight or
25 branched chain alkyl moiety having one to six carbons
26 and having in addition one double bond, of either E or
27 Z stereochemistry where applicable. This term would
28 include, for example, an alpha, beta-unsaturated
29 methylene, vinyl, 1-propenyl, 1- and 2-butenyl and
30 2-methyl-2-propenyl.

31

32

33

1 The term "cycloalkyl" refers to a saturated
2 alicyclic moiety having from 3 to 8 carbon atoms
3 and includes, for example, cyclopropyl, cyclobutyl,
4 cyclopentyl and cyclohexyl.

5

6 The term "cycloalkenyl" refers to an unsaturated
7 alicyclic moiety having from 3 to 8 carbon atoms
8 and includes, for example, cyclopropenyl, cyclobutenyl,
9 cyclopentenyl and cyclohexenyl.

10

11 The term "heterocyclylthiomethyl" refers to a
12 methyl group substituted by a heterocyclic thiol for
13 example pyridine-2-thiol, pyridine-4-thiol,
14 thiophene-2-thiol or pyrimidine-2-thiol.

15

16 The term "substituted", as applied to a phenyl or other
17 aromatic ring, means substituted with up to four
18 substituents each of which independently may be C₁-C₆
19 alkyl, C₁-C₆ alkoxy, hydroxy, thiol, C₁-C₆ alkylthiol,
20 amino, halo (including fluoro, chloro, bromo and iodo),
21 trifluoromethyl, nitro, -COOH, -COONH₂ or -CONHRA,
22 wherein RA represents a C₁-C₆ alkyl group or the
23 characteristic side chain of an amino acid such as
24 alanine, valine, leucine, isoleucine, phenylalanine,
25 tryptophan, methionine, glycine, serine, threonine,
26 cysteine, tyrosine, asparagine, glutamine, aspartic
27 acid, glutamic acid, lysine, arginine or histidine.

28

29 The term "amino acid side chain" means a characteristic
30 side chain attached to the -CH(NH₂)(COOH) moiety in the
31 following R or S amino acids: glycine, alanine, valine,
32 leucine, isoleucine, phenylalanine, tyrosine,

33

1 tryptophan, serine, threonine, cysteine, methionine,
2 asparagine, glutamine, lysine, histidine, arginine,
3 glutamic acid and aspartic acid.

4
5 There are several chiral centres in the compounds
6 according to the invention because of the presence of
7 asymmetric carbon atoms. The presence of several
8 asymmetric carbon atoms gives rise to a number of
9 diastereomers with the appropriate R or S
10 stereochemistry at each chiral centre. General formula
11 I and, where appropriate, all other formulae in this
12 specification are to be understood to include all such
13 stereoisomers and mixtures (for example racemic
14 mixtures) thereof. Compounds in which the chiral centre
15 adjacent the substituent R^3 has S stereochemistry are
16 preferred.

17
18 Further or other preferred compounds include those in
19 which, independently or in any combination:

20
21 R^1 represents a hydrogen atom or a C_1 - C_4 alkyl (such
22 as methyl), phenylthiomethyl or
23 heterocyclylthiomethyl (such as
24 thiophenylthiomethyl) group;

25 R^2 represents a C_3 - C_6 alkyl (such as isobutyl or
26 n-pentyl) group;

27 R^3 represents a benzyl, 4-(C_1 - C_6)alkoxyphenylmethyl
28 or benzyloxy benzyl group;

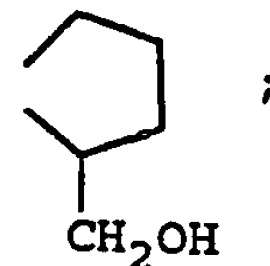
29 R^4 represents a hydrogen atom or

30 R^4 and R^5 together represent a group

31

32

33



1

2 n has the value 1, 2 or 3; and/or

3 A represents a hydroxy, methoxy, acetoxy,
4 acetylamino, thioethyl or N-pyrrolidone group.

5

6 Particularly preferred compounds include:

7

8 1. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
9 phenylalanine-N-(2-hydroxyethyl)-amide;

10

11 2. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
12 phenylalaninyl-proline;

13

14 3. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
15 phenylalanine-N-(2-hydroxyethyl)-N-methylamide;

16

17 4. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
18 phenylalaninyl-D-prolinol;

19

20 5. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
21 phenylalaninyl-L-prolinol;

22

23 6. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
24 phenylalanine-N-(5-N-methyl-pentylcarboxamide)
25 amide;

26

27 7. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
28 phenylalanine-N-(2-ethyl thioethyl) amide;

29

30 8. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
31 phenylalanine-N-(2-methoxyethyl) amide;

32

33

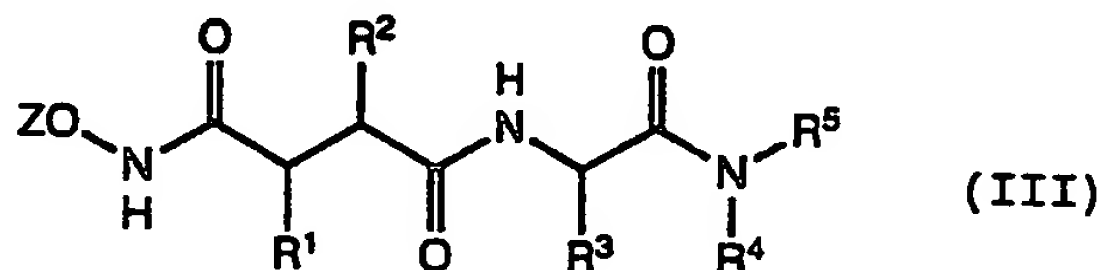
- 1 9. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
2 phenylalanine-N-(2-N-acetylethyl) amide;
3
- 4 10. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
5 phenylalanine-N-(3-(2-pyrrolidone)propyl) amide;
6
- 7 11. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
8 phenylalanine-N-(3-(2-pyrrolidone)propyl) amide
9 sodium salt;
10
- 11 12. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
12 phenylalanine-N-(2-acetoxyethyl) amide;
13
- 14 13. [4-(N-Hydroxyamino)-2R-isobutyl-3S-
15 methylsuccinyl]-L-phenylalanine-N-(3-(2-
16 pyrrolidone)propyl) amide;
17
- 18 14. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
19 succinyl]-L-phenylalanine-N-methyl-N-(2-hydroxy-
20 ethyl) amide;
21
- 22 15. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
23 succinyl]-L-phenylalanine-N-(2-hydroxyethyl)
24 amide;
25
- 26 16. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
27 succinyl]-L-phenylalaninyl-D-prolinol;
28
- 29 17. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
30 succinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)pro-
31 pyl) amide sodium salt;
32
33

1 and free bases, free acids and salts thereof, where
 2 appropriate. Compounds 13 and 10 are especially
 3 preferred and compound 13 is the most preferred.

4
 5 Compounds of general formula I may be prepared by any
 6 suitable method known in the art and/or by the
 7 following process, which itself forms part of the
 8 invention.

9
 10 According to a second aspect of the invention, there is
 11 provided a process for preparing a compound of general
 12 formula I as defined above, the process comprising:

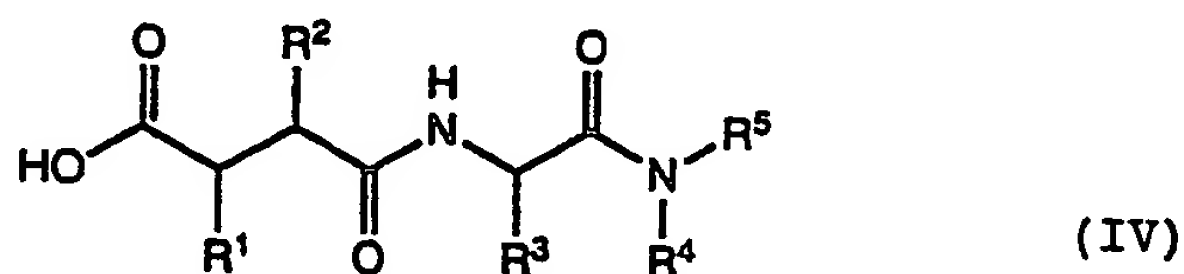
13
 14 (a) deprotecting (for example by hydrogenating) a
 15 compound of general formula III



16
 17
 18
 19
 20
 21 wherein:

22
 23 R^1 , R^2 , R^3 , R^4 and R^5 are as defined in general
 24 formula I and Z represents a protective group,
 25 such as a benzyl group; or

26
 27 (b) reacting a compound of general formula IV



28
 29
 30
 31
 32
 33 wherein:

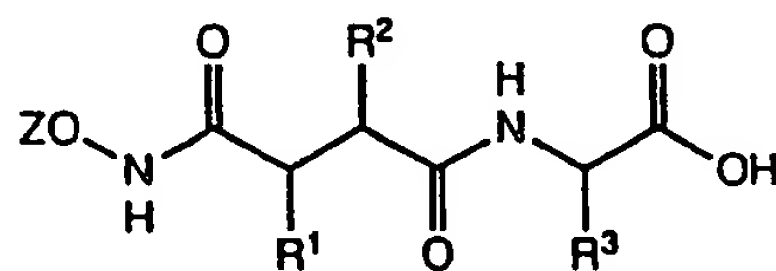
1
2 R^1 , R^2 , R^3 , R^4 and R^5 are as defined in general
3 formula I,
4

5 with hydroxylamine or a salt thereof; and
6

7 (c) optionally after step (a) or step (b) converting a
8 compound of general formula I into another compound of
9 general formula I.
10

11 Compounds of general formula I which are sulfoxides or
12 sulphones can be derived from thiol compounds of
13 general formula I by oxidation. Alternatively, thiols
14 of general formula III or IV can be oxidised.
15 Compounds of general formula I which are disulphides
16 (ie compounds wherein R^1 represents SR^X) may be derived
17 from thiol compounds of general formula I by mild
18 oxidation with, for example, iodine in methanol.
19

20 A compound of general formula III can be obtained by
21 coupling, for example by conventional coupling
22 techniques, a compound of general formula IV with an
23 O-protected (for example benzyl) hydroxylamine or by
24 reacting a compound of general formula V
25



(V)

32 wherein:
33

34 R^1 , R^2 and R^3 are as defined in general formula I
35 and Z represents a protective group such as
36 benzyl,

1 with a compound of general formula VI

2

3



(VI)

4

5 A compound of general formula V may be prepared by
6 hydrolysis in the presence of a base such as sodium
7 hydroxide of a compound of general formula VII

8

9

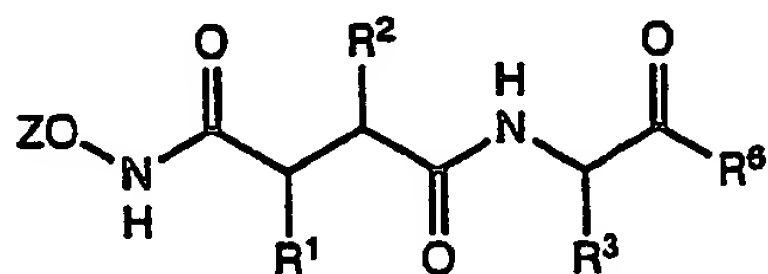
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(VII)

15

wherein:

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22 A compound of general formula VII may be prepared by
23 coupling, for example by conventional coupling
24 techniques, a compound of general formula VIII with an
25 O-protected (for example benzyl) hydroxylamine

26

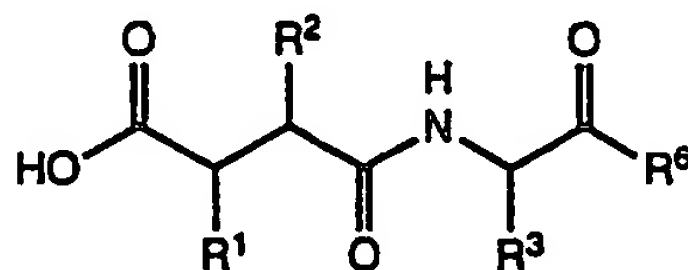
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(VIII)

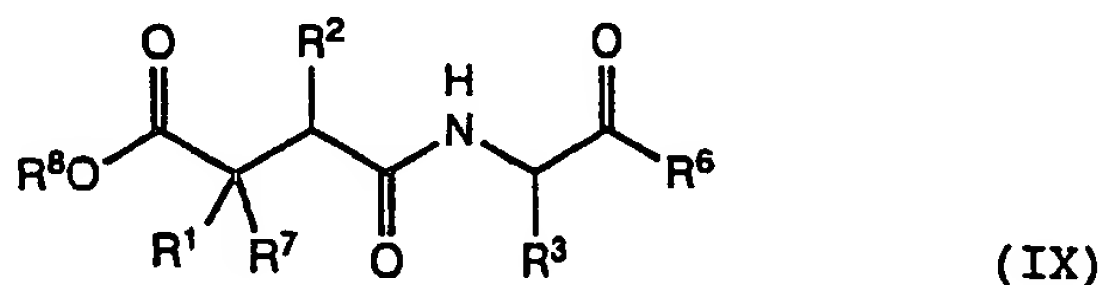
32

wherein:

33

1 R^1 , R^2 and R^3 are as defined in general formula I
 2 and R^6 represents a C_1 - C_6 alkoxy, benzyloxy or
 3 substituted benzyloxy group.

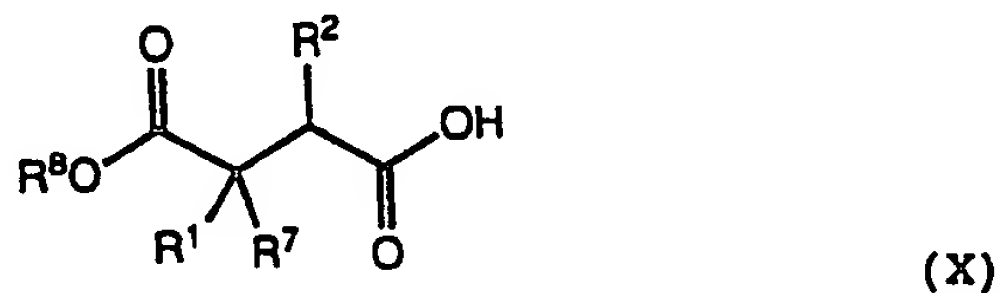
4
 5 A compound of general formula VIII may be prepared by
 6 hydrogenating and (eg thermally) decarboxylating a
 7 compound of general formula IX



14 wherein:

15
 16 R^1 , R^2 and R^3 are as defined in general formula I,
 17 R^8 represents a C_1 - C_6 alkyl or benzyl group, R^6
 18 represents a C_1 - C_6 alkoxy, benzyloxy or
 19 substituted benzyloxy group and R^7 represents a
 20 C_1 - C_6 alkoxycarbonyl or benzyloxycarbonyl group.

21
 22 A compound of general formula IX may be prepared by
 23 reacting a substituted acid of general formula X



30 wherein:

31
 32
 33

1 R^1 and R^2 are as defined in general formula I, R^8
2 represents a C_1 - C_6 alkyl or benzyl group and R^7
3 represents a C_1 - C_6 alkoxy carbonyl or
4 benzyloxy carbonyl group, with

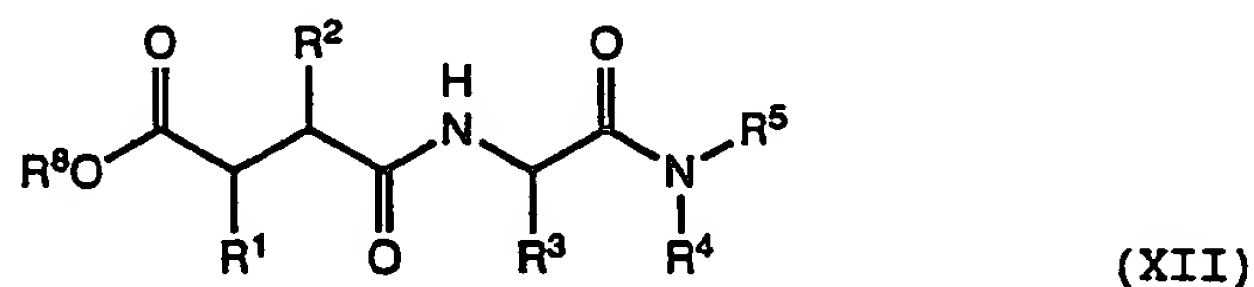
5
6 an amino acid derivative of general formula (XI)



11 wherein:

12 R^3 is as defined in general formula I and R^6
13 represents a C_1 - C_6 alkoxy, benzyloxy or
14 substituted benzyloxy group.

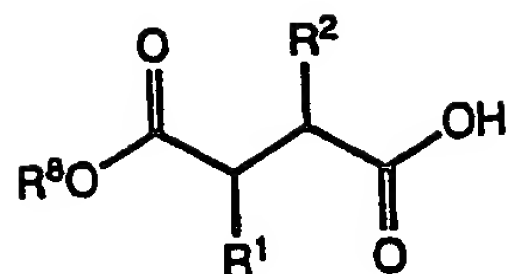
15
16 Alternatively, a compound of general formula IV can be
17 prepared by de-esterifying (for example hydrolysing,
18 under acid or base catalysis) a compound of general
19 formula XII



23
24
25
26 wherein:

27
28 R^1 , R^2 , R^3 , R^4 and R^5 are as defined in general
29 formula I and R^8 represents a C_1 - C_6 alkyl or
30 benzyl group.

1 A compound of general formula XII can be prepared in a
2 manner analogous to the preparation of a compound of
3 formula IX by reacting a substituted acid of general
4 formula XIII
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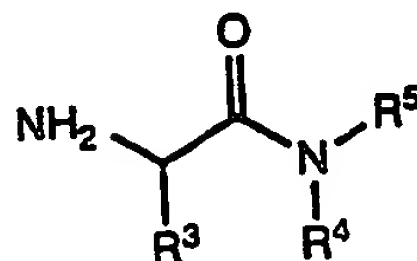


(XIII)

wherein:

R¹ and R² are as defined in general formula I and
R₈ represents a C₁-C₆ alkyl or benzyl group,

with an amino acid derivative of general formula XIV

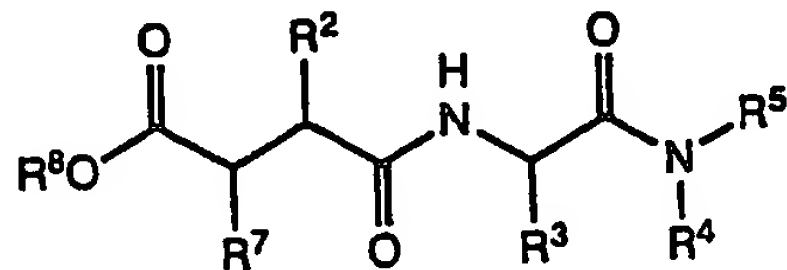


(XIV)

wherein:

R³, R⁴ and R⁵ are as defined in general formula I.

In a further synthetic variant, a compound of general formula X as defined above wherein R¹ represents a hydrogen atom can be reacted with a compound of general formula XIV to produce a compound of general formula XV



(XV)

1 wherein:

2

3 R^2 , R^3 , R^4 and R^5 are as defined in general
4 formula I, R^8 represents a C_1 - C_6 alkyl or benzyl
5 group and R^7 represents a C_1 - C_6 alkoxy carbonyl or
6 benzyloxycarbonyl group.
7

8 A compound of general formula XV wherein R^8
9 represents benzyl and R^1 represents benzyloxycarbonyl
10 may be hydrogenated to the malonic acid, then treatment
11 with aqueous formaldehyde and piperidine gives a
12 compound of formula XVI
13

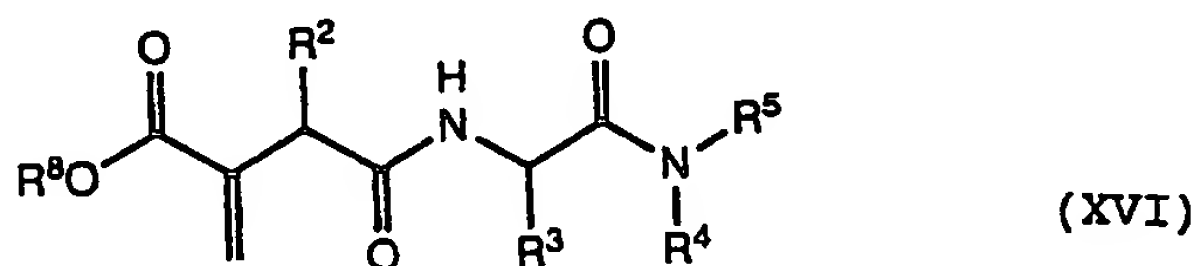
14

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18



19 wherein:

20

21 R^2 , R^3 , R^4 and R^5 are as defined in general
22 formula I.
23

24 Compounds of general formula XVI, by treatment with the
25 appropriate thiols give the acids of general formula IV
26 where R^1 is a substituted thiomethyl derivative.
27 Thiomethyl derivatives can be oxidised to sulphoxides
28 and sulphones as appropriate.
29

30 The starting materials (compounds of general
31 formulae IX, X, XIII and XIV) and reagents described
32 above are either commercially available or may be
33 produced by conventional processes from commercially

1 available materials. For example, when R^1 represents a
 2 hydrogen atom, the substituted acid of general formula
 3 XIII may be prepared by reaction of an aldehyde XVII



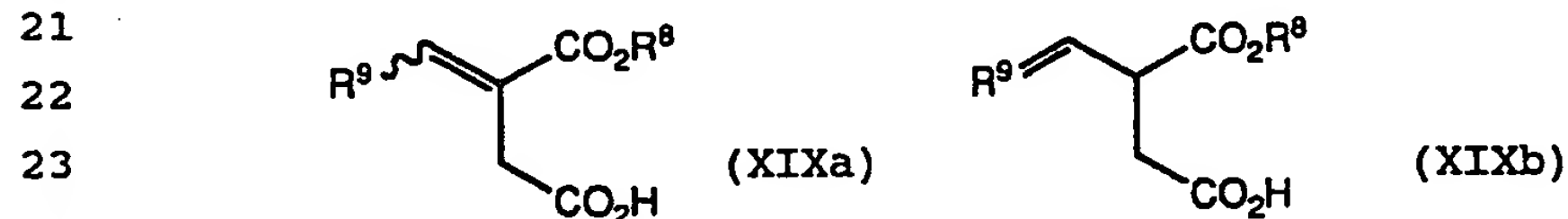
6
 7 wherein R^9 represents a hydrogen atom or a C_1-C_5 alkyl
 8 C_1-C_5 alkenyl, phenyl (C_1-C_5) alkyl, cycloalkyl (C_1-C_5)
 9 alkyl or cycloalkenyl (C_1-C_5) alkyl group, with a
 10 succinate derivative of general formula XVIII,



13
 14 wherein:

15
 16 R^8 represents a C_1-C_6 alkyl or benzyl group

17
 18 under base catalysis to give a mixture of acids of
 19 general formulae XIXa and XIXb

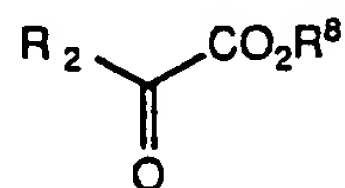


25 which by hydrogenation, esterification and hydrolysis
 26 can be converted to the acids of the general formula
 27 XIII.

28
 29 Alternatively an ester of general formula XX may be
 30 reacted with an ester stabilised phosphorane of general
 31 formula XXI

32

33

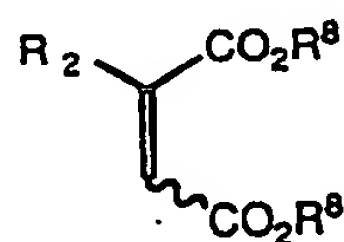


(XX)



(XXI)

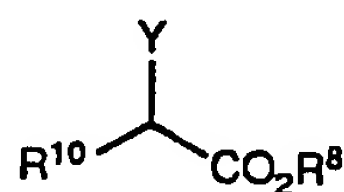
to yield a compound of general formula XXII



(XXII)

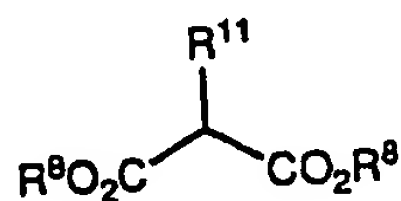
wherein R^8 represents a C_1 - C_6 alkyl group, which can be further converted by hydrogenation to the acids of general formula XIII.

In addition the substituted esters may be prepared by reacting an ester of the general formula XXIII



(XXIII)

wherein Y represents halo and R^8 is as defined above and R^{10} is either R^1 or R^2 as defined above, with a malonate derivative of the general formula XXIV



(XXIV)

wherein R^{11} is R^2 or R^1 as defined above, and the alternative to that substituent employed in the halo ester.

1 Compounds of general formulae III and IV are valuable
2 intermediates in the preparation of compounds of
3 general formula I. According to a third aspect of the
4 invention, there is therefore provided a compound of
5 general formula III. According to a fourth aspect of
6 the invention, there is provided a compound of general
7 formula IV.

8
9 As mentioned above, compounds of general formula I are
10 useful in human or veterinary medicine as they are
11 active inhibitors, of metalloproteases involved in
12 tissue degradation.

13
14 According to a fifth aspect of the invention, there is
15 provided a compound of general formula I for use in
16 human or veterinary medicine, particularly in the
17 management (by which is meant treatment of prophylaxis)
18 of disease involving tissue degradation, in particular
19 rheumatoid arthritis, and/or in the promotion of wound
20 healing.

21
22 According to a sixth aspect of the invention, there is
23 provided the use of a compound of general formula I in
24 the preparation of an agent for the management of
25 disease involving tissue degradation, particularly
26 rheumatoid arthritis, and/or in the promotion of wound
27 healing. Compounds of general formula I can therefore
28 be used in a method of treating disease involving
29 tissue degradation, particularly rheumatoid arthritis,
30 and/or in a method of promoting wound healing, the
31 method in either case comprising administering to a
32 human or animal patient an effective amount of a
33 compound of general formula I.

1
2 The potency of compounds of general formula I to act
3 as inhibitors of collagenase (a metalloprotease
4 involved in tissue degradation) was determined by the
5 procedure of Cawston and Barrett, (Anal. Biochem., 99,
6 340-345, 1979) and their potency to act as inhibitors
7 of stromelysin was determined using the procedure of
8 Cawston et al (Biochem. J., 195, 159-165 1981), both of
9 which techniques are to be described more fully in the
10 examples and, to the extent that the law allows, are
11 incorporated by reference herein.

12
13 According to a seventh aspect of the invention, there
14 is provided a pharmaceutical or veterinary formulation
15 comprising a compound of general formula I and a
16 pharmaceutically and/or veterinarily acceptable
17 carrier. One or more compounds of general formula I may
18 be present in association with one or more non-toxic
19 pharmaceutically and/or veterinarily acceptable
20 carriers and/or diluents and/or adjuvants and if
21 desired other active ingredients.

22
23 According to an eighth aspect of the invention, there
24 is provided a process for the preparation of a
25 pharmaceutical or veterinary formulation in accordance
26 with the seventh aspect, the process comprising
27 admixing a compound of general formula I and a
28 pharmaceutically and/or veterinarily acceptable
29 carrier.

30
31 Compounds of general formula I may be formulated for
32 administration by any route and would depend on the
33 disease being treated. The may be in the form of

1 tablets, capsules, powders, granules, lozenges, liquid
2 or gel preparations, such as oral, nasal, topical,
3 or sterile parenteral solutions or suspensions.

4
5 Tablets and capsules for oral administration may be in
6 unit dose presentation form, and may contain
7 conventional excipients such as binding agents, for
8 example syrup, acacia, gelatin, sorbitol, tragacanth,
9 or polyvinyl-pyrrolidone; fillers for example
10 lactose, sugar, maize-starch, calcium phosphate,
11 sorbitol or glycine; tableting lubricant, for example
12 magnesium stearate, talc, polyethylene glycol or
13 silica; disintegrants, for example potato starch, or
14 acceptable wetting agents such as sodium lauryl
15 sulphate. The tablets may be coated according to
16 methods well known in normal pharmaceutical practice.

17
18 Oral liquid preparations may be in the form of, for
19 example, aqueous or oily suspensions, solutions,
20 emulsions, syrups or elixirs, or may be presented as a
21 dry product for reconstitution with water or other
22 suitable vehicle before use. Such liquid
23 preparations may contain conventional additives such
24 as suspending agents, for example sorbitol, syrup,
25 methyl cellulose, glucose syrup, gelatin,
26 hydrogenated edible fats; emulsifying agents, for
27 example lecithin, sorbitan monooleate, or acacia;
28 non-aqueous vehicles (which may include edible
29 oils), for example almond oil, fractionated coconut
30 oil, oily esters such as glycerine, propylene glycol,
31 or ethyl alcohol; preservatives, for example methyl or

32
33

1 propyl p-hydroxybenzoate or sorbic acid, and if
2 desired conventional flavouring or colouring
3 agents.
4

5 The dosage unit involved in oral administration may
6 contain from about 1 to 250 mg, preferably from about
7 25 to 250 mg, of a compound of general formula I. A
8 suitable daily dose for a mammal may vary widely
9 depending on the condition of the patient and will
10 ultimately depend on the judgement of the physician or
11 veterinarian. However, a dose of a compound of general
12 formula I of about 0.1 to 300mg/kg body weight,
13 particularly from about 1 to 100 mg/kg body weight may
14 be appropriate.
15

16 For topical application to the skin the drug may be
17 made up into a cream, lotion or ointment. Cream or
18 ointment formulations that may be used for the drug are
19 conventional formulations well known in the art, for
20 example, as described in standard text books of
21 pharmaceutics such as the British Pharmacopoeia.
22

23 For topical applications to the eye, the drug may be
24 made up into a solution or suspension in a suitable
25 sterile aqueous or non-aqueous vehicle. Additives,
26 for instance buffers such as sodium metabisulphite or
27 disodium edeate; preservatives including bactericidal
28 and fungicidal agents, such as phenyl mercuric
29 acetate or nitrate, benzalkonium chloride or
30 chlorohexidine, and thickening agents such as
31 hypromellose may also be included.
32
33

1 The dosage employed for the topical administration
2 will, of course, depend on the size of the area being
3 treated. For the eyes each dose will be typically in
4 the range from 10 to 100 mg of the compound of general
5 formula I.

6
7 The active ingredient may also be administered
8 parenterally in a sterile medium. The drug
9 depending on the vehicle and concentration used, can
10 either be suspended or dissolved in the vehicle.
11 Advantageously, adjuvants such as a local anaesthetic,
12 preservative and buffering agents can be dissolved in
13 the vehicle.

14
15 For use in the treatment of rheumatoid arthritis the
16 compounds of this invention can be administered by
17 the oral route or by injection intra-articularly into
18 the affected joint. The daily dosage for a 70 kg
19 mammal will be in the range of 10 mg to 1 gram of a
20 compound of general formula I.

21
22 The following examples illustrate the invention, but
23 are not intended to limit the scope in any way.

24
25 The following abbreviations have been used in the
26 Examples:-

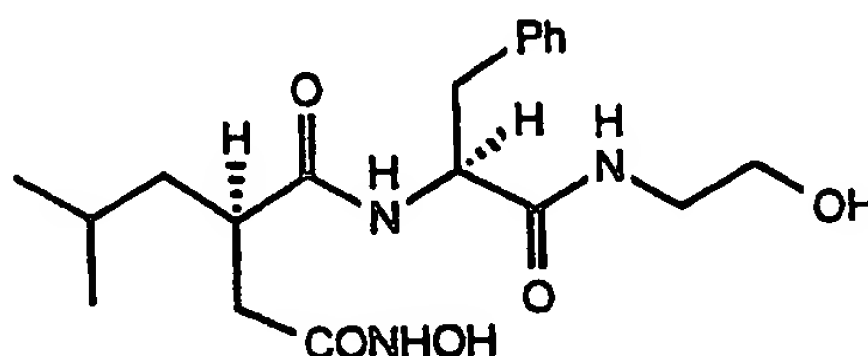
27
28 DCC - Dicyclohexylcarbodiimide
29 DCM - Dichloromethane
30 DCU - Dicyclohexylurea
31 DIPE - Diisopropyl ether
32 DMF - N,N-dimethylformamide
33 HOBT - Hydroxybenztriazole

- 1 NMM - N-Methylmorpholine
2 TFA - Trifluoroacetic acid
3 THF - Tetrahydrofuran
4 WSCDI - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide
5

EXAMPLES

Example 1

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
alanine-N-(2-hydroxyethyl)-amide



(a) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutyl-
succinyl]-L-phenylalanine methyl ester

Benzyl (2-benzyloxycarbonyl-5-methyl-3R-tert-butoxy-
carbonyl)-hexanoate (52g, 115 mmol) was stirred at room
temperature with 5% water in TFA (250 ml) for 1.5h.
After this time the TFA was evaporated under reduced
pressure then the residue was azeotroped with toluene
(3 x 250 ml).

The crude acid from this reaction was dissolved in
DCM/DMF (4:1), then HOBT (16g, 118 mmol), NMM (12g,
118 mmol) and WSCDI (22g, 115 mmol) were added at room
temperature. After 20 minutes a further equivalent of
NMM (12g, 118 mmol) was added followed by

1 L-phenylalanine methyl ester hydrochloride (23g, 107
2 mmol). This solution was stirred overnight and then
3 concentrated under vacuum. The oily residue was
4 dissolved in DCM then washed with 10% citric acid
5 (2x250 ml), with 10% sodium bicarbonate (2x250 ml) and
6 once with saturated brine (250 ml). The organic
7 layer was dried (sodium sulphate), filtered then the
8 solvent removed under reduced pressure to give the
9 title compound as an oil (50.9g, 79%).

10

11 δ_H (250MHz, $CDCl_3$, 3:1 mixture of diastereomers)
12 Major diastereomer 0.72 (3H, d, $J=6$ Hz, $CH(CH_3)_2$),
13 0.74 (3H, d, $J=6$ Hz, $CH(CH_3)_2$), 0.80 - 1.00 (2H, m,
14 $CHCH_2 + CHMe_2$), 1.40 - 1.60 (2H, m, $CHCH_2 + CHCH_2$),
15 2.95 (1H, dd, $J=14,6$ Hz, CH_2Ph), 3.07 (1H, dd, $J=14,5$
16 Hz, CH_2Ph), 3.64 (3H, s, CO_2Me), 3.82 (1H, d, $J=10$
17 Hz, $CH(CO_2Bn)_2$), 4.82 (1H, m, $CHCO$), 5.0 - 5.2 (2H,
18 m, OCH_2Ph), 6.2 (1H, d, $J=8$ Hz, NH), and 7.10 - 7.40
19 (15H, m, Ph). Minor diastereomer shows 0.63 (3H, d,
20 $J=6$ Hz, $CH(CH_3)_2$), 0.68 (3H, d, $J=6$ Hz, $CH(CH_3)_2$),
21 3.67 (3H, s, CO_2Me), and 3.75 (1H, d, $J=8$ Hz,
22 $CH(CO_2Bn)_2$)

23

24 (b) [4-Hydroxy-2R-isobutylsuccinyl]-L-phenylalanine
25 methyl ester

26

27 The product from above (50.9g, 91 mmol) was dissolved
28 in ethanol (100ml) and stirred at room temperature
29 with activated charcoal pellets for 1h. 10% Palladium
30 on charcoal (20g) in ethyl acetate was slurried into
31 the ethanolic solution. Cyclohexene (20ml) in ethanol
32 (100ml) was added and the mixture was brought to reflux
33 for 5h. The reaction mixture was filtered to remove

1 the catalyst, then the solvents evaporated under
2 reduced pressure to leave a yellow oil (29.8g). This
3 oil was taken up in xylene (500ml) and heated at
4 reflux for 10 minutes. The xylene was removed under
5 reduced pressure to leave the crude material as an oil
6 (26.5g).

7

8 (c) [4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-
9 phenylalanine methyl ester

10

11 The crude acid (26.5g, 79mmol) was dissolved in
12 DCM/DMF (4:1, 500ml), then NMM (9.6g, 95mmol), HOBT
13 (12.8g 95mmol) and WSCDI (18.2g, 95mmol) added and the
14 mixture stirred at room temperature until tlc
15 indicated complete conversion to the activated ester
16 (about 10 minutes). To this solution containing the
17 active ester was added benzylhydroxylamine
18 hydrochloride (15.2g, 95mmol) and a further equivalent
19 of NMM (9.6g, 95mmol) in the solvent mixture (80ml).
20 After stirring at room temperature overnight DCM
21 (250ml) was added then the mixture washed with citric
22 acid (2x250ml), 10% sodium bicarbonate solution
23 (2x250ml) and brine (250ml) then finally dried over
24 sodium sulphate. The solution was filtered and the
25 solvent removed under reduced pressure to give an oil
26 (27.2g) which was purified by column chromatography
27 using ether as an eluant to give the title compound
28 (11g, 23.7mmol, 30%).

29

30 δ_H (250MHz, $CDCl_3$) 0.84 (6H, m, $CH(CH_3)_2$), 1.16 (1H,
31 m, $CHMe_2$), 1.51 (2H, m, CH_2CHMe_2), 2.1 - 2.4 (2H, bm,
32 $CH_2CONHOBN$), 2.73 (1H, m, CH_2CHCO), 3.06 (2H, d, J= 6

33

1 Hz, CH_2Ph), 3.68 (3H, s, CO_2Me), 4.8 - 5.0 (3H, s + m,
2 OCH_2Ph and COCHNH), 6.25 (1H, d, $J = 8$ Hz, NH), 7.05 -
3 7.50 (10H, m, Ph), and 8.66 (1H, s, NHOBn).
4

5 (d) [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-
6 phenylalanine
7

8 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenylala-
9 nine methyl ester (9.5g, 21mmol) was dissolved in
10 methanol (200ml) and lithium hydroxide solution
11 (0.5N, 84ml, 42mmol) was added with stirring at room
12 temperature. When the reaction was complete, as judged
13 from tlc, the methanol was removed by evaporation and
14 the remaining aqueous phase was acidified to pH1 with
15 citric acid. The precipitated solid was filtered off
16 and dried, while the filtrate was extracted with DCM
17 (500ml) and dried over sodium sulphate. Solvent
18 removal from the organic phase left an oil (5.38g)
19 which could be recrystallised from diisopropyl ether
20 and methanol to give material which was identical with
21 the solid which precipitated during acidification.
22 These two batches were combined to give the title
23 compound (6.40g, 15mmol, 71%)
24

25 m.p. 161-162°C
26

27 ν_{max} (KBr) 3300, 3020, 2980, 1710, 1650, 1630, 1550,
28 1265, 740, and 700 cm^{-1}
29

30 δ_{H} (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$) 0.80 - 0.87 (7H, m), 1.50
31 (2H, bm), 2.0 - 2.1 (2H, m), 2.91 - 3.14 (2H, m,
32 CH_2Ph), 4.77 (2H, s, OCH_2Ph), and 7.18 - 7.36 (10H, m,
33 Ph).

1
2 δ_C (62.9MHz, D_6 -DMSO) 174.1, 173.1, 167.7, 137.9,
3 129.2-126.4, 76.9, 53.3, 40.7, 39.9, 36.8, 35.8, 25.3,
4 23.5, and 22.1

5
6 (e) [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
7 alanine-N-(2-hydroxyethyl)-amide

8
9 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenylala-
10 nine (7.50g, 17.6mmol) was dissolved in DCM (100ml)
11 and cooled in ice. Triethylamine (1.96g, 19.4mmol)
12 was added together with ethylchloroformate (2.10g,
13 19.4mmol) and after 10 minutes ethanolamine (1.55g,
14 21.1mmol) in DCM (10ml) was added. After 3h at room
15 temperature the reaction mixture was diluted with ethyl
16 acetate then washed with sodium bicarbonate solution
17 and brine, and finally dried over sodium sulphate.
18 Solvent removal under reduced pressure gave the
19 crude benzyl hydroxamate which was recrystallised from
20 ethyl acetate/hexane (2.6g, 5.5mmol)

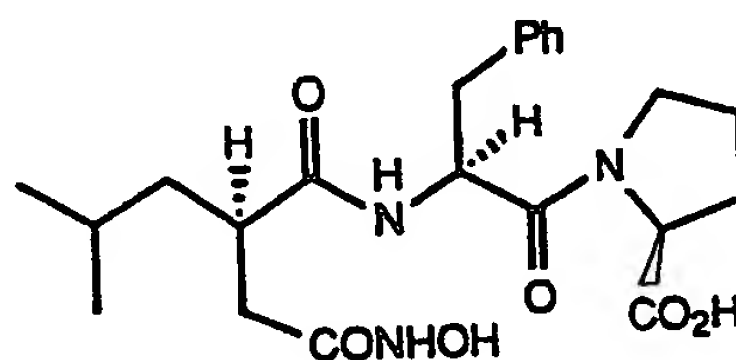
21
22 The crude material from above was dissolved in
23 cyclohexene/ethanol (10% solution, 55ml), 10% palladium
24 on charcoal (250mg) was added then the mixture refluxed
25 until starting material had disappeared by tlc (ca.
26 30 minutes). The catalyst was removed by filtration,
27 and the solvent removed under reduced pressure to
28 leave a solid which could be recrystallised from
29 methanol and DIPE. The required product (1.54g,
30 4.00mmol, 74%) was collected by filtration.

31
32 m.p. 156-158°C
33

1 $[\alpha]_D = -21.5$ (c=1, MeOH)
2
3 $\nu_{\max}(\text{KBr})$ 3300, 2950, 1650, 1550, and 700cm^{-1}
4
5 δ_H (250MHz, CDCl_3) 0.72 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$),
6 0.77 (3H, d, $J=6$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.95 (1H, m, CHCH_2),
7 1.28 (2H, m, $\text{CH}(\text{CH}_3)_2 + \text{CHCH}_2$), 1.92 (2H, m,
8 CH_2CONHOH), 2.61 (1H, bm, CHCO), 2.80 (1H, dd, $J=$
9 14,12 Hz, CH_2Ph), 3.00 - 3.20 (3H, m, $\text{NCH}_2 + \text{CH}_2\text{Ph}$),
10 4.41 (1H, m, NCHCO), 4.65 (1H, bt, OH), 7.22 (5H, m,
11 Ph), 7.86 (1H, t, $J=6$ Hz, CONHCH_2), 8.07 (1H, d, $J=8$
12 Hz, CONH), and (8.76 (1H, s, NHOH).
13
14 δ_C (62.9MHz, $\text{D}_6\text{-DMSO}$) 174.0, 171.2, 138.3, 129.2,
15 128.1, 126.2, 59.8, 54.0, 41.6, 37.3, 35.8, 25.3, 23.5,
16 and 22.0.
17
18 Analysis calculated for $\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}_5$
19 Requires C 60.14 H 7.70 N 11.07
20 Found C 59.97 H 7.68 N 11.10
21

22 Example 2

23
24 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
25 alaninyl-proline
26
27



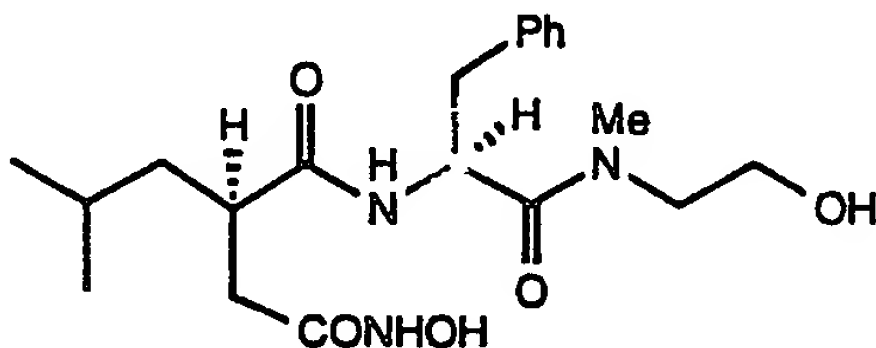
1 Using the procedure described in Example 1e
2 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
3 alanine (1.8g, 4.2mmol) was coupled with L-proline
4 benzyloxy ester hydrochloride (1.21g, 5.00mmol) then the
5 product hydrogenated to give the title compound (34mg,
6 78.5 μ mol, 2%)

7
8 δ_H (250MHz, D_6 -DMSO) 0.78 (6H, 2xd, $J=6$ Hz, $CH(CH_3)_2$),
9 0.96 (1H, m, CH_2CHMe_2), 1.36 (2H, m, CH_2CHMe_2), 1.86
10 (6H, m, $CH_2CONHOH$ and NCH_2CH_2), 2.79 (1H, dd, $J=$
11 15,9 Hz, CH_2Ph), 2.97 (1H, dd, $J=14,4.6$ Hz, CH_2Ph),
12 3.43 and 3.64 (2H, m, CH_2N), 4.23 (1H, m, $NCHCO_2H$),
13 4.66 (1H, $NHCHCONH$), 7.30 (5H, m, Ph), 8.24 (1H, d, $J=$
14 8Hz, NH), and 8.69 (1H, s, OH)

15
16 δ_C (62.9MHz, D_6 -DMSO) 174.2, 173.4, 169.4, 167.2,
17 137.8, 129.4, 128.2, 126.4, 59.8, 51.8, 48.5, 40.5,
18 39.8, 36.6, 35.8, 28.8, 25.4, 24.7, 23.5, and 22.0

19
20 Example 3

21
22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
23 alanine-N-(2-hydroxyethyl)-N-methylamide.
24



32 Using the procedure described in Example 1e
33 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
alanine (0.5g, 1.17mmol) was coupled with

1 N-methylethanolamine (100mg, 1.29mmol) then the
2 product hydrogenated to give the title compound (97mg,
3 0.25 mmol, 21%)

4

5 m.p. 136.0 -137.0°C

6

7 $[\alpha]_D = +1.1$ (c=1, MeOH)

8

9 $\nu_{\max}(\text{KBr})$ 3600 - 3100, 2960, 1680, 1560, 940, 750, and
10 700 cm^{-1}

11

12 δ_H (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$, 1:1) 0.74 (6H, m, $\text{CH}(\text{CH}_3)_2$),
13 1.00 (1H, m, CH_2CHMe_2), 1.36 (2H, m, CH_2CHMe_2), 2.00
14 (2H, m, CH_2NHOH), 2.60 - 3.00 (3H, m, + 3H, 2xs), 3.39
15 (2H, m), 4.42 -4.70 (1H, m, OH), 4.80 - 5.00 (1H, m,
16 CH_2Ph), 7.14 (5H, m, Ph), 7.97 (1H, d, J= 7Hz, NH), and
17 8.50 (1H, s, NHOH)

18

19

20

21 δ_C (62.9MHz, $\text{D}_6\text{-DMSO}$, 1:1 Mixture of Rotamers)
22 173.9, 173.8, 171.3, 170.3, 167.5, 138.2, 137.9,
23 129.4, 128.1, 126.4, 126.3, 58.7, 58.4, 51.2, 50.2,
24 50.0, 49.7, 40.7, 40.5, 39.8, 37.7, 37.4, 36.0, 35.9,
25 33.9, 25.4, 23.5, 23.4, and 22.1.

26

27 Example 4

28

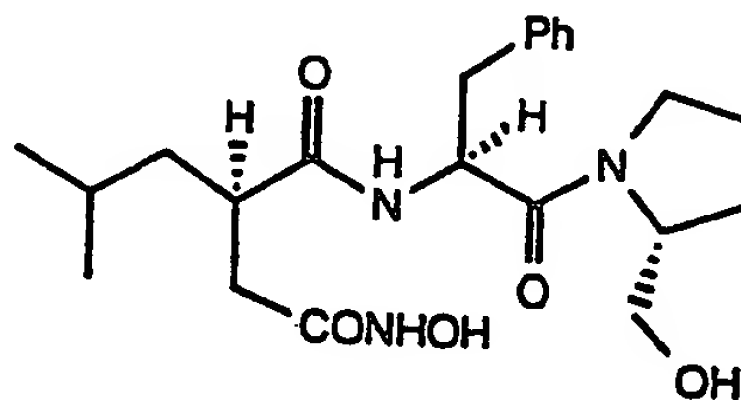
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31

32

33



1
2 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
3 alaninyl-D-prolinol.
4

5 Using the procedure described in Example 1e
6 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
7 alanine (0.5g, 1.17mmol) was coupled with
8 R-pyrrolidine methanol (130mg, 1.29mmol) then the
9 product hydrogenated to give the title compound (150mg,
10 0.36 mmol, 31%)
11

12 m.p. 150.0 -155.0°C
13

14 $[\alpha]_D = +21.4$ (c=1, MeOH)
15

16 $\nu_{\max}(\text{KBr})$ 3300, 2960, 1650, 1620, 1450, 1050, and 700
17 cm^{-1}
18

19 δ_H (250MHz, D_6 -DMSO) 0.80 (6H, m, $\text{CH}(\text{CH}_3)_2$), 1.10 - 2.1
20 (14H, m), 2.6 - 3.2 (6H, m), 4.6 (2H, m), 7.2 (5H, m,
21 Ph), 8.3 (1H, d, J= 8Hz, NH), and 8.7 (1H, s, NHOH).
22

23 δ_C (62.9MHz, D_6 -DMSO), Major Rotamer shows 179.4,
24 175.0, 172.6, 142.8, 129.4, 128.1, 126.4, 60.7, 58.7,
25 52.1, 46.4, 41.1, 37.1, 35.8, 26.5, 25.5, 23.5, 23.2,
26 22.1, and 21.4; minor rotamer shows 179.4, 175.6,
27 172.6, 143.4, 129.4, 128.1, 126.2, 62.7, 61.3, 45.4,
28 40.5, 37.2, 35.8, 27.6, 25.6, 23.4, 22.1, and
29 21.4.
30
31
32
33

1 Example 5

2

3

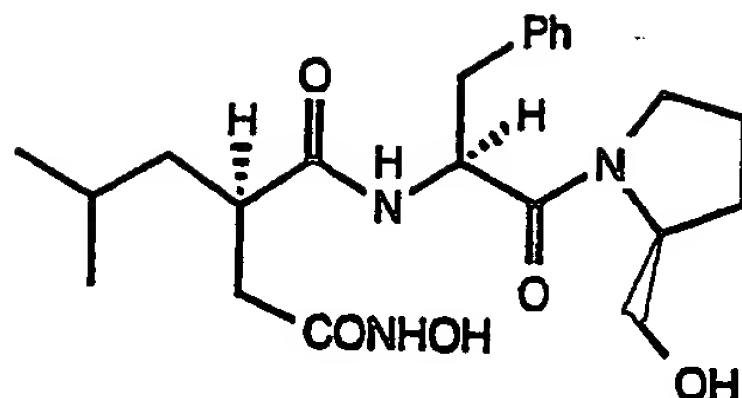
4

5

6

7

8



9 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
10 alaninyl-L-prolinol.

11

12 Using the procedure described in Example 1e
13 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
14 alanine (0.5g, 1.17mmol) was coupled with
15 S-pyrrolidine methanol (130mg, 1.29mmol) then the
16 product hydrogenated to give the title compound (106mg,
17 0.25 mmol, 22%)

18

19 m.p. 154.0 -155.0°C

20

21 $[\alpha]_D = -0.3$ (c=1, MeOH)

22

23 $\nu_{\max}(\text{KBr})$ 3300, 2960, 1650, 1620, 1550, 1450, 1050,
24 and 700 cm^{-1}

25

26 δ_H (250MHz, $\text{CDCl}_3/\text{D}_6\text{-DMSO}$, 1:1) 0.80 (6H, m, $\text{CH}(\text{CH}_3)_2$),
27 1.4 - 1.8 (14H, m), 2.7 - 3.6 (4H, m), 4.6 - 4.9 (3H,
28 m), and 7.2 (5H, m, Ph).

29

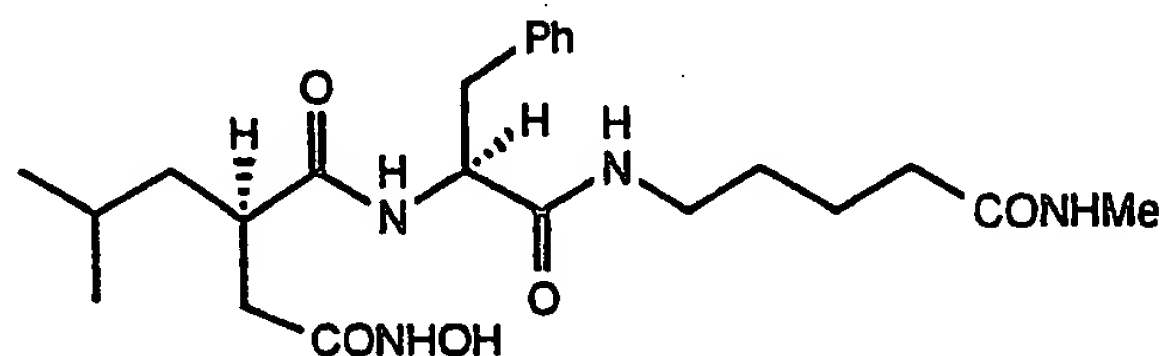
30 δ_C (62.9MHz, $\text{D}_6\text{-DMSO}$), Major rotamer shows 174.0,
31 169.8, 167.6, 137.6, 129.4, 129.2, 128.5, 61.8, 58.7,
32 52.2, 48.6, 40.8, 39.8, 37.5, 35.8, 28.5, 25.4, 23.5,
33 23.4, and 22.2; Minor rotamer 174.1, 169.7, 167.6,

1 137.6, 129.4, 128.3, 126.9, 61.8, 58.5, 52.2, 45.4,
2 40.8, 39.7, 38.9, 35.8, 27.3, 25.3, 23.5, 23.4, and
3 22.4.

4
5 Analysis calculated for $C_{22}H_{33}N_3O_5$
6 Required C 62.99 H 7.93 N 10.02
7 Found C 62.74 H 7.85 N 9.79

8
9 Example 6

10
11 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
12 alanine-N-(5-N-methyl-pentylcarboxamide) amide.



21 Using the procedure described in Example 1e
22 [4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
23 alanine (0.4g, 1.00 mmol) was coupled with
24 N-methyl-(5-aminopentylcarboxamide) trifluoroacetic acid
25 salt (1.00mmol) then the product hydrogenated to give
26 the title compound (137mg, 0.25 mmol, 30%)

27 m.p. 149 - 151°C

28
29 $[\alpha]_D = -13.7^\circ$ (c=1.3, MeOH)

30
31 $\nu_{\max}(\text{KBr})$ 3290, 2950, 1655, 1640, and 1545 cm^{-1}

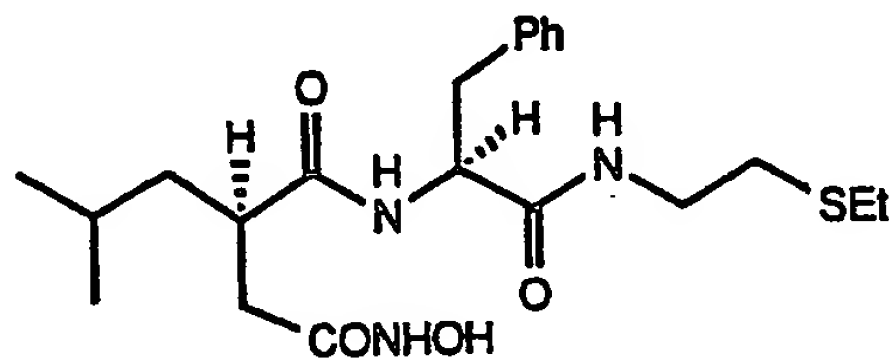
32
33

1 δ_H (250MHz, D_6 -DMSO) 0.72 (3H, d, $J=6$ Hz, $CH(CH_3)_2$),
2 0.77 (3H, d, $J=6$ Hz, $CH(CH_3)_2$) 1.02 (1H, m), 1.31 (6H,
3 m), 2.02 (4H, m), 2.54 (3H, d, $J=5$ Hz), 2.61 (1H, m),
4 2.84 (1H, dd, $J=9,14$ Hz), 3.01 (3H, m), 4.39 (1H, m),
5 7.21 (5H, m), 7.72 (1H, m), 7.82 (1H, t, $J=2$ Hz), 8.09
6 (1H, d, $J=8$ Hz), and 8.76 (1H, bs)

7
8 δ_C (62.9MHz, D_6 -DMSO) 173.9, 172.5, 170.9, 167.6,
9 138.3, 129.2, 128.1, 126.2, 54.1, 40.8, 38.7, 38.4,
10 37.5, 35.8, 35.1, 28.7, 25.5, 25.3, 23.5, 22.7, and
11 22.0.

12
13 Example 7

14
15 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
16 alanine-N-(2-ethyl thioethyl) amide.



25 Using the procedure described in Example 1e
26 4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
27 alanine (0.5g, 1.17mmol) was coupled with
28 2-(thioethyl)-1-aminoethane hydrochloride (183mg,
29 1.29mmol) then the product hydrogenated to give the
30 title compound (163 mg).

31 m.p. 169 - 171°C

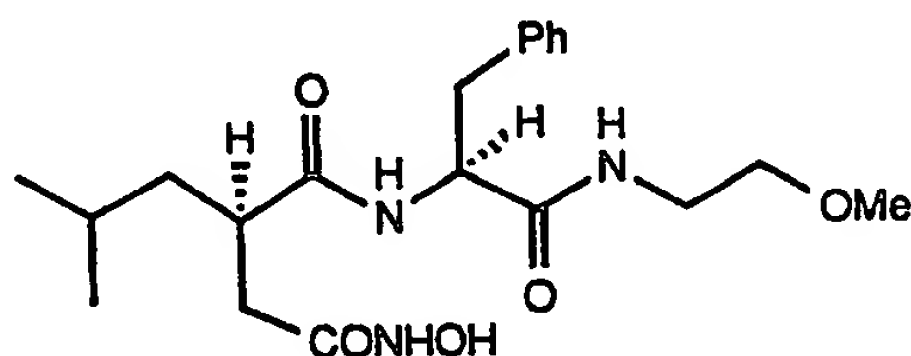
32
33 $[\alpha]_D = -19.7^\circ$ (c=1, MeOH)

1
2 $\nu_{\max}(\text{KBr})$ 3280, 2950, 2920, 1655, 1640, and 1540 cm^{-1}
3
4 δ_{H} (250MHz, D_6 -DMSO) 0.72 (3H, d, $J=6\text{Hz}$), 0.77 (3H,
5 d, $J=7\text{Hz}$), 0.95 (1H, m), 1.17 (3H, t, $J=7\text{Hz}$), 1.29
6 (2H, m), 1.93 (2H, m), 2.49 (4H, m), 2.62 (1H, m), 2.82
7 (1H, dd, $J=14,10\text{Hz}$), 3.03 (1H, dd, $J=14,5\text{Hz}$), 3.19
8 (2H, m), 4.40 (1H, m), 7.22 (5H, m), 8.07 (2H, m), 8.75
9 (1H, s), and 10.39 (1H, s).

10
11 δ_{C} (62.9MHz, D_6 -DMSO) 174.0, 171.1, 167.7, 138.3,
12 129.2, 128.1, 126.3, 54.1, 40.8, 40.7, 38.8, 37.3,
13 35.8, 30.0, 25.3, 24.9, 23.5, 22.0, and 14.9.

14
15 Example 8

16
17 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
18 alanine-N-(2-methoxyethyl) amide.



27 Using the procedure described in Example 1e
28 [4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
29 alanine (0.43g, 1.0 mmol) was coupled with
30 O-methylethanolamine (90mg, 1.20mmol) then the product
31 hydrogenated to give the title compound (92mg, 0.23
32 mmol, 27%)

33 m.p. 151 - 153°C

1

2 $\nu_{\max}(\text{KBr})$ 3280, 2960, 1640, 1540, 1120, and 700 cm^{-1}

3

4 δ_{H} (250MHz, D_6 -DMSO) 0.73 (3H, d, $J=6\text{Hz}$), 0.78 (3H,
5 d, $J=6\text{Hz}$), 0.95 (1H, m), 1.29 (2H, m), 1.92 (2H, m),
6 2.61 (1H, m), 2.85 (1H, dd, $J=14,10\text{ Hz}$), 3.00 (1H,
7 dd, $J=14,4\text{ Hz}$), 3.20 (1H, m), 3.27 (1H, m), 3.33 (3H,
8 s), 4.43 (1H, m), 7.22 (5H, m), 7.91 (1H, m), and 8.08
9 (1H, d, $J=8\text{Hz}$).

10

11 δ_{C} (62.9MHz, D_6 -DMSO) 174.0, 171.2, 167.6, 138.3,
12 129.2, 128.1, 126.2, 70.5, 58.1, 54.0, 37.4, 35.8,
13 25.3, 23.4, and 21.9.

14

15 Analysis calculated for $\text{C}_{20}\text{H}_{31}\text{N}_3\text{O}_5 \cdot 0.3\text{H}_2\text{O}$

16 Required C 60.22 H 7.99 N 10.53

17 Found C 60.24 H 7.80 N 10.54

18

19

20 Example 9

21

22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
23 alanine-N-(2-N-acetyylethyl) amide.

24

25

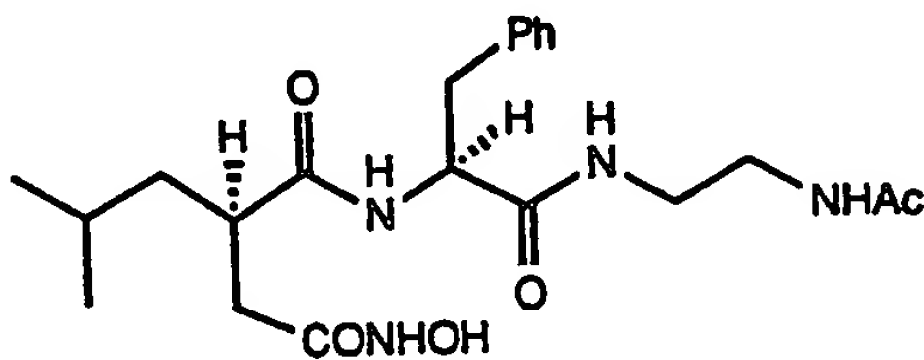
26

27

28

29

30



31 Using the procedure described in Example 1e

32 [4-(N-Benzoyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-

33 alanine (0.43g, 1.0 mmol) was coupled with

1 N-acetyl-1,3-ethyldiamine (133mg, 1.30mmol) then the
2 product hydrogenated to give the title compound (176mg,
3 0.42 mmol, 42%)

4
5 m.p. 167 - 169°C

6
7 $[\alpha]_D = -4.2^\circ$ (c=1, MeOH)

8
9 $\nu_{\max}(\text{KBr})$ 3280, 2930, 1640, 1540, and 700 cm^{-1}

10
11 δ_H (250MHz, D_6 -DMSO) 0.72 (3H, d, J= 6Hz), 0.77 (3H,
12 d, J= 6Hz), 1.30 (2H, t, J= 10 Hz), 1.78 (3H, s), 2.06
13 (1H, m), 2.18 (1H, m), 2.87 (2H, m), 3.04 (2H, s),
14 3.13 (2H, q, J= 6 Hz), 3.36 (1H, m), 7.21 (5H, m),
15 7.78 (1H, s), 7.98 (1H, s), 8.08 (1H, d, J= 8Hz) and
16 8.77 (1H, s).

17
18 δ_C (62.9MHz, D_6 -DMSO) 174.8, 171.2, 169.4, 167.8,
19 138.3, 129.2, 128.1, 128.2, 54.2, 37.2, 35.8, 25.3,
20 23.4, 22.8 and 22.01.

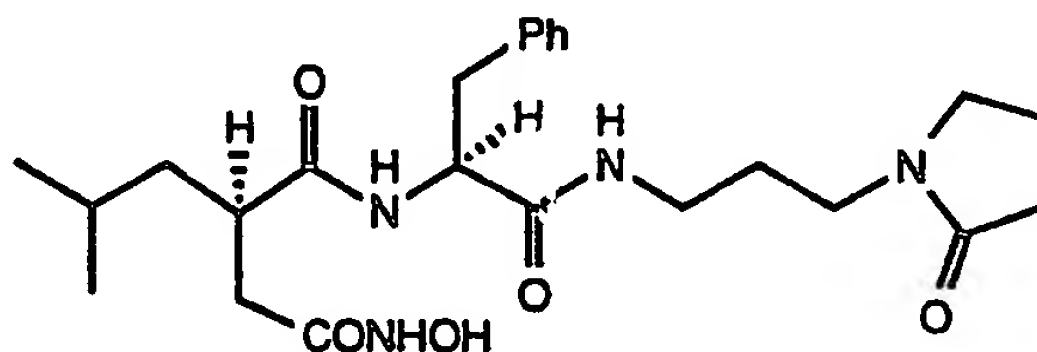
21
22 Analysis calculated for $C_{21}H_{32}N_4O_5 \cdot 0.4H_2O$

23 Required C 58.97 H 7.73 N 13.10

24 Found C 59.07 H 7.60 N 12.90

25
26 Example 10

27
28 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
29 alanine-N-(3-(2-pyrrolidone)propyl) amide.

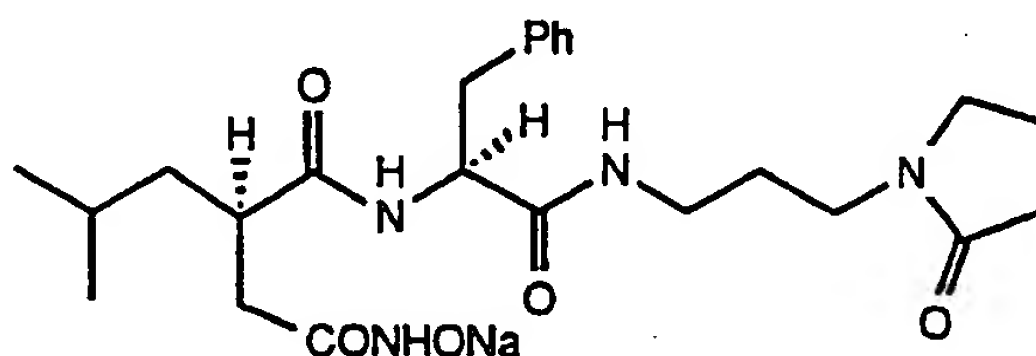


1
2
3
4 Using the procedure described in Example 1e
5 [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-phenyl-
6 alanine (0.43g, 1.0 mmol) was coupled with
7 1-(3-aminopropyl)-2-pyrrolidinone (180mg, 1.26mmol)
8 then the product hydrogenated to give the title
9 compound (280mg, 0.61 mmol, 61%)
10
11 m.p. 174 - 176°C
12
13 $[\alpha]_D = -8.7^\circ$ (c=1.35, MeOH)
14
15 $\nu_{\max}(\text{KBr})$ 3270, 3220, 2960, 1660, 1640, and 1525 cm^{-1}
16
17 δ_H (250MHz, D_6 -DMSO) 0.72 (3H, d, J= 6Hz), 0.77 (3H,
18 d, J= 6Hz), 0.98 (1H, m), 1.33 (2H, m), 1.52 (2H, m),
19 1.87 - 2.06 (4H, m), 2.20 (2H, t, J= 8Hz), 2.62 (1H,m),
20 2.83 (1H, dd, J= 14,9 Hz), 2.99 (1H, t, J= 8 Hz), 3.10
21 (2H, t, J= 7 Hz), 3.28 (2H, m), 4.39 (1H, m), 7.22 (5H,
22 m), 7.91 (1H, m), 8.09 (1H, d, J= 8Hz), 8.80 (1H, bs),
23 and 10.4 (1H,bs).
24
25 δ_C (62.9MHz, D_6 -DMSO) 174.0, 171.0, 167.7, 138.3,
26 129.2, 128.1, 126.2, 54.2, 46.6, 40.9, 40.6, 39.6,
27 38.7, 37.4, 36.5, 35.8, 30.6, 26.9, 25.3, 23.4, 22.1
28 and 17.7.
29
30
31
32
33

1 Analysis calculated for $C_{24}H_{36}N_4O_5$
2 Required C 62.59 H 7.88 N 12.16
3 Found C 62.67 H 7.96 N 12.22
4

5 Example 11
6

7 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
8 alanine-N-(3-(2-pyrrolidone)propyl) amide sodium salt.
9



15
16 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
17 alanine-N-(3-(1-pyrrolidone)propyl) amide (50mg,
18 0.109mmol) was dissolved in methanol (20ml) and sodium
19 hydroxide solution (1.0M, 0.11ml) added to give a
20 homogeneous solution. The methanol was removed under
21 reduced pressure then the residual aqueous solution
22 freeze dried to give the title compound (52mg,
23 0.108mmol, 99%).
24

25 δ_H (250MHz, D_6 -DMSO) 0.66 (3H, d, $J=6$ Hz), 0.75 (3H,
26 d, $J=6$ Hz), 0.94 (1H, m), 1.04 (2H, m), 1.56 (2H, m),
27 1.92 (3H, m), 2.08 (1H, dd, $J=14,8$ Hz), 2.14 (2H, t, $J=$
28 8Hz), 2.45 (1H, m), 2.83 (1H, dd, $J=14,10$ Hz), 3.03
29 (2H, d, $J=6$ Hz), 3.13 (4H, m), 3.23 - 3.48 (6H, m),
30 4.35 (1H, m), 7.20 (5H, m), 8.20 (1H, d, $J=8$ Hz), and
31 8.53 (1H, s).
32
33

1 Example 12

2

3 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
4 alanine-N-(2-acetoxyethyl) amide.

5

6

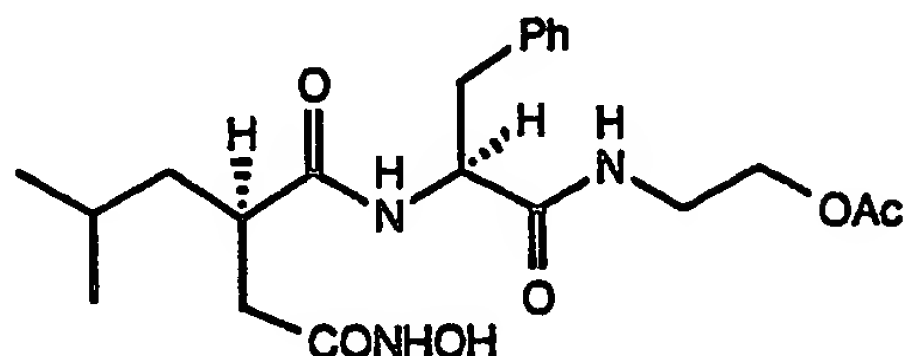
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9

10

11



12 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-phenyl-
13 alanine-N-(2-hydroxyethyl)-amide (Example 1e, 148mg,
14 0.32 mmol) was mixed with dimethylamino pyridine (40
15 mg, 0.33 mmol) in DCM at -30° , then acetic anhydride
16 (32 mg, 0.32 mmol) was added and the reaction stirred
17 for 25 min. The mixture was partitioned between ethyl
18 acetate and water, the organic layer separated and
19 washed sequentially with sodium bicarbonate, citric
20 acid and brine then dried over sodium sulphate.
21 Purification by column chromatography (ethyl acetate
22 as eluant) gave protected material (130mg) which was
23 hydrogenated as before to give the title compound
24 (62mg, 0.15mmol, 46%).

25

26 m.p. $136 - 137^{\circ}\text{C}$

27

28 $[\alpha]_{\text{D}} = -19.9^{\circ}$ (c=1.2, MeOH)

29

30 ν_{max} (KBr) 3280, 2955, 1745, 1660, 1645, 1550 and 1235
31 cm^{-1}

32

33

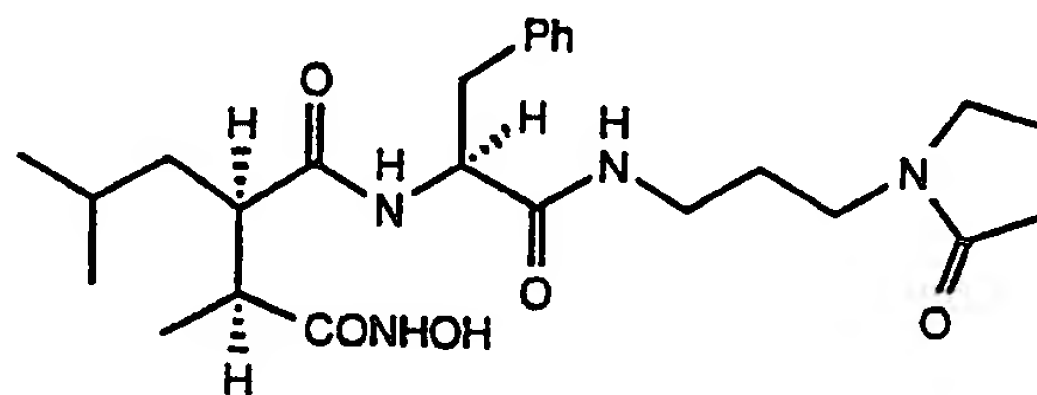
1 δ_H (250MHz, $CDCl_3/D_6$ -DMSO) 0.71 (3H, d, J= 6Hz), 0.75
 2 (3H, d, J= 6Hz), 0.99 (1H, m), 1.2 - 1.4 (2H, m), 1.96
 3 (1H, m + 3H, s), 2.11 (1H, dd, J= 14,8 Hz), 2.59
 4 (1H,m), 2.86 (1H, dd, J= 14,9 Hz), 3.06 (1H, dd, J=
 5 14,5 Hz), 3.30 (2H, m), 3.95 (2H, t, J= 6 Hz), 4.44
 6 (1H, m), 7.16 (5H, m), and 8.00 (2H, m).

7
 8 δ_C (62.9MHz, D_6 -DMSO) 174.1, 171.3, 170.1, 168.0,
 9 138.0, 129.1, 127.9, 126.0, 78.8, 62.4, 41.0, 40.9,
 10 37.8, 37.3, 35.8, 25.3, 23.1, 21.9 and 20.7.

11
 12 Analysis calculated for $C_{21}H_{31}N_3O_6 \cdot 0.4H_2O$
 13 Required C 58.84 H 7.48 N 9.80
 14 Found C 58.91 H 7.33 N 9.55

15
 16 Example 13

17
 18 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
 19 phenylalanine-N-(3-(2-pyrrolidone)propyl) amide.
 20



27 (a) 2S-tert-Butyl(3,3-di(benzyloxycarbonyl)-2,5-
 28 dimethyl)hexanoate

29
 30 Benzyl (2-benzyloxycarbonyl-5-methyl) pentanoate
 31 (100g, 0.29 mol) was dissolved in dry DMF (150 ml) and
 32 cooled while potassium tert-butoxide (31.1g, 0.28
 33 mol) was added portionwise over 10 minutes. This was

1 then stirred for a further 1 hour until the solid had
2 dissolved. To the resultant mixture, cooled to -20 to
3 -30°, was added tert-butyl 2S-bromopropionate (60.6g,
4 0.29 mol) in dry DMF (50 ml) over about 30 minutes.
5 The reaction mixture was left at -20° for 3 days then
6 5° for 1 day before working up by partitioning between
7 ether and ammonium chloride solution. The aqueous
8 layer was extracted three times with ether then the
9 combined organic layers washed with brine and dried.
10 Solvent removal gave the crude title compound (141.2g,
11 0.30 mol, 100%)

12
13 $[\alpha]_D = 33.0^\circ$ (c=1.00, MeOH)

14
15 δ_H (250MHz, CDCl₃) 0.82 (6H, d, J= 6 Hz), 1.28 (3H, t,
16 J= 7 Hz), 1.40 (9H, s), 1.46 (2H, m), 1.76 (1H, m),
17 1.92 (1H, dd, J= 6,2 Hz), 5.11 (4H, m), and 7.27 (10H,
18 m)

19
20 δ_C (62.9MHz, CDCl₃) 172.7, 170.3, 135.3, 128.2, 80.8,
21 66.9, 58.7, 45.2, 42.5, 27.8, 24.4, 23.9, 23.8, and
22 14.3.

23
24 (b) 2S,3R tert-Butyl (3-carboxylic acid-2,5-dimethyl)-
25 hexanoate

26
27 The crude material from Example 13a (141.2g, 0.30
28 mol) was taken up in ethanol (200 ml) and refluxed
29 with activated charcoal (10g) for 1 hour to remove
30 catalyst poisons. Cyclohexene (100 ml) and 10%
31 palladium on charcoal (14g) was added and the mixture
32
33

1 refluxed for 2 hours. The catalyst was removed by
2 filtration through celite and the solvent removed under
3 reduced pressure.

4
5 The residual oil was taken up in xylene (200 ml) and
6 refluxed for 30 minutes to effect decarboxylation.
7 The solution was extracted with sodium carbonate
8 solution (3 x 300 ml) this aqueous solution washed
9 with ether then acidified to pH 5 with citric acid. The
10 acidic solution was extracted with ethyl acetate (3 x
11 200 ml) then dried over sodium sulphate. Solvent
12 removal then gave the crude title compound (53.2g, 0.22
13 mol, 73%)

14
15 $[\alpha]_D = 8.0^\circ$ (c=1.00, MeOH)

16
17 δ_H (250MHz, $CDCl_3$) 0.76 (6H, 2 x d, J= 6 Hz), 1.02
18 (3H, m), 1.28 (9H, s), 1.46 (2H, m), 2.42 (1H, m), and
19 2.58 (1H, m)

20
21 δ_C (62.9MHz, $CDCl_3$) 173.9, 128.7, 46.5, 43.0, 39.1,
22 27.8, 26.2, 23.5, 21.4, and 14.9.

23
24 (c) [4-(tert-Butyloxy)-2R-isobutyl-3S-methylsuccinyl]-
25 L-phenylalanine methyl ester

26
27 The crude acid from Example 13b (45.0g, 0.18 mol) was
28 dissolved in DCM, then HOBT (24.9g, 0.18 mol) added.
29 The solution was cooled and NMM (18g, 0.18 mol),
30 phenylalanine methyl ester hydrochloride (36.1g, 0.17
31 mol) and DCC (38g, 0.18 mol) were added. This
32 solution was stirred overnight, concentrated under
33 vacuum then the precipitated DCU filtered off. The

1 oily residue was dissolved in ethyl acetate then
2 washed with 10% citric acid (2x250 ml), with 10%
3 sodium bicarbonate (2x250 ml) and once with saturated
4 brine (250 ml). The organic layer was dried (sodium
5 sulphate), filtered then the solvent removed under
6 reduced pressure to give the crude title compound as
7 an oil (80.6g, 0.20 mol, 120%).

8
9 (d) [4-(N-Benzoyloxyamino)-2R-isobutyl-3S-methyl-
10 succinyl]-L-phenylalanine methyl ester

11
12 The crude tert-butyl ester (80.6g, 0.20 mol) was
13 dissolved in trifluoroacetic acid/water (95:5, 85 ml)
14 and left at 4°C overnight. The solution was taken up
15 in DCM, the aqueous layer re-extracted with DCM then
16 the combined organic layers extracted with sodium
17 bicarbonate (5 x 50 ml). The basic layer was
18 acidified to pH 4 with citric acid then extracted
19 with ethyl acetate. Drying and solvent removal gave
20 the related acid (40.4g, 0.115 mol, 69%).

21
22 The crude acid (40.4g, 115mmol) was dissolved in
23 DCM/DMF (4:1, 500ml), then HOBT (17.18g 127mol) and
24 DCC (26.1g, 127mmol) were added and the mixture
25 stirred at room temperature until tlc indicated
26 complete conversion to the activated ester (about 10
27 minutes). To this solution containing the active
28 ester was added benzylhydroxylamine (15.6g,
29 127mmol). After stirring at room temperature overnight
30 DCM was removed under vacuum, the residue taken up in
31 ethyl acetate then precipitated DCU removed by
32 filtration. The solution was washed with citric acid
33 (2x250ml), 10% sodium bicarbonate solution (2x250ml)

1 and brine (250ml) then finally dried over sodium
2 sulphate. The solvent was removed under reduced
3 pressure to give an oil (45.6g) which was purified by
4 recrystallisation from ethanol and DIPE (7.66g, 17mmol,
5 15%).

6
7 δ_H (250MHz, $CDCl_3$) 0.47 (3H, d, J= 7 Hz), 0.74 (3H, d,
8 J= 6 Hz), 0.83 (3H, d, J= 6 Hz), 1.35 (2H, m), 1.94
9 (1H, dd, J= 7,11 Hz), 2.38 (1H, m), 2.83 (1H, dd, J=
10 14,11 Hz), 3.06 (1H, dd, J= 5,14 Hz), 3.29 (3H, s),
11 3.62 (3H, s), 4.58 (1H, m), 4.77 (2H, s), 7.20 (5H, m),
12 7.38 (5H, s), and 8.49 (1H, d, J= 8 Hz).

13
14 (e) [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methyl-
15 succinyl]-L-phenylalanine

16
17 [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methyl-
18 succinyl]-L-phenylalanine methyl ester (7.66g,
19 17mmol) was dissolved in methanol (120ml) and sodium
20 hydroxide solution (1.0 M, 20.3ml, 20.3mmol) was added
21 with stirring at room temperature. When the reaction
22 was complete, as judged from tlc, the methanol was
23 removed by evaporation the residue extracted with ether
24 to remove starting material (2.1g, 4.6 mmol, 21%
25 recovered). The aqueous phase was acidified to pH4
26 with citric acid and extracted with ethyl acetate to
27 give the title compound (5.88g, 13.3mmol, 79%).

28
29 δ_H (250MHz, $CDCl_3$) 0.47 (3H, d, J= 7 Hz), 0.74 (3H, d,
30 J= 6 Hz), 0.83 (3H, d, J= 6 Hz), 1.35 (2H, m), 1.94
31 (1H, dd, J= 7,11 Hz), 2.38 (1H, m), 2.83 (1H, dd, J=

32
33

1 14,11 Hz), 3.06 (1H, dd, J= 5,14 Hz), 3.29 (3H, s),
2 3.62 (3H, s), 4.58 (1H, m), 4.77 (2H, s), 7.20 (5H, m),
3 7.38 (5H, s), and 8.49 (1H, d, J= 8 Hz).
4

5 (f) [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
6 succinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)propyl)
7 amide.
8

9 [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
10 phenyl alanine (400 mg, 0.9 mmol), HOBt (134 mg, 1.0
11 mmol) and NMM (102 mg, 1.0 mmol) were dissolved in
12 DCM/DMF (4:1, 10ml) and cooled in ice.
13 1-(3-Aminopropyl)-2-pyrrolidinone (142 mg, 1.0 mmol)
14 was added together with WSCDI (192 mg, 1.0 mmol).
15 After 2h at room temperature the reaction mixture was
16 diluted with ethyl acetate then washed with sodium
17 bicarbonate solution and brine, then dried over sodium
18 sulphate. Solvent removal under reduced pressure gave
19 the crude benzyl hydroxamate which was recrystallised
20 from ethyl acetate/hexane (385 mg, 0.68 mmol)
21

22 The material from above was dissolved in
23 cyclohexene/ethanol (10% solution, 20ml), 10%
24 palladium on charcoal (50mg) was added then the
25 mixture refluxed until starting material had
26 disappeared by tlc (ca. 30 minutes). The catalyst was
27 removed by filtration, and the solvent removed under
28 reduced pressure to leave a solid which could be
29 recrystallised from ethyl acetate/ethanol. The
30 required product (243 mg, 0.51 mmol, 76%) was
31 collected by filtration.
32

33 m.p. 198 - 200°C

1

2 $[\alpha]_D = 73.0^\circ$ (c=1.00, MeOH)

3

4 $\nu_{\max}(\text{KBr})$ 3380, 2960, 1635, 1345, 1030, and 715 cm^{-1}

5

6 δ_H (250MHz, D_6 -DMSO) 0.44 (3H, d, J= 7Hz, CHCH_3), 0.72
7 (3H, d, J= 6Hz, $\text{CH}(\text{CH}_3)_2$), 0.80 (3H, d, J= 6Hz,
8 $\text{CH}(\text{CH}_3)_2$), 1.32 (2H, m), 1.53 (2H, q, J= 7 Hz), 1.92
9 (4H, m), 2.21 (2H, t, J= 8 Hz), 2.37 (1H, m), 2.79 (1H,
10 m), 2.93 (1H, d, J= 5 Hz), 3.01 (2H, m), 3.13 (2H, t, J=
11 7Hz), 3.32 (6H, m), 4.54 (1H, m), 7.25 (5H, m), 7.80
12 (1H, t, J= 7 Hz), 8.20 (1H, d, J= 8Hz, NH), 8.69 (1H,
13 s), and 10.36 (1H, s).

14

15 δ_C (62.9MHz, D_6 -DMSO) 174.0, 173.9, 171.4, 171.2,
16 138.2, 129.3, 128.0, 126.3, 54.6, 47.0, 46.7, 37.7,
17 36.3, 30.7, 27.3, 25.4, 24.3, 21.5, 17.7 and 16.1.

18

19 Analysis calculated for $\text{C}_{25}\text{H}_{38}\text{N}_4\text{O}_5 \cdot 0.5\text{H}_2\text{O}$

20 Required C 62.20 H 7.93 N 11.50

21 Found C 63.27 H 8.07 N 11.81

22

23 Example 14

24

25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
26 L-phenylalanine-N-methyl-N-(2-hydroxyethyl) amide.

27

28

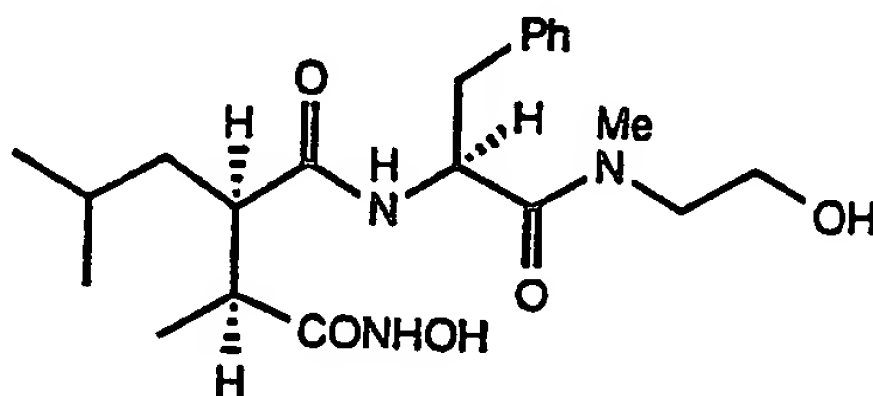
29

30

31

32

33



1 Using the procedure described in Example 13f
2 [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
3 -phenylalanine (0.4g, 0.91mmol) was coupled with
4 N-methylethanolamine (75mg, 1.00mmol) then the product
5 hydrogenated to give the title compound (100mg, 0.25
6 mmol, 27%)

7

8 m.p. 182 - 183°C

9

10 $[\alpha]_D = 27.0^\circ$ (c=0.25, MeOH)

11

12 $\nu_{\max}(\text{KBr})$ 3400, 3240, 2960, 1660, and 1545 cm^{-1}

13

14 δ_H (250MHz, D_6 -DMSO, mixture of rotamers) 0.46 + 0.54
15 (3H, d, J= 6Hz, CHCH_3), 0.72 + 0.79 (6H, m, $\text{CH}(\text{CH}_3)_2$),
16 1.3 (2H, m), 2.0 (1H, m), 2.4 (1H, m), 2.81 + 3.03
17 (3H, s, $\text{N}(\text{CH}_3)$), 2.8 - 3.9 (8H, m), 5.0 (1H, m), 7.27
18 (5H, m), 8.35 (1H, d, J= 8Hz, NH), and 8.73 (1H, m).

19

20 δ_C (62.9MHz, D_6 -DMSO, mixture of rotamers), 173.3,
21 173.2, 171.6, 171.4, 171.0, 138.3, 138.0, 129.4,
22 128.1, 128.0, 126.4, 126.3, 58.8, 58.5, 51.4, 50.2,
23 50.1, 49.9, 46.7, 40.1, 37.4, 37.1, 36.2, 33.9, 25.5,
24 25.4, 24.2, 24.1, 21.8, 21.7, 16.3, and 16.2.

25

26 Analysis calculated for $\text{C}_{21}\text{H}_{33}\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O}$

27 Required C 59.28 H 8.29 N 9.87

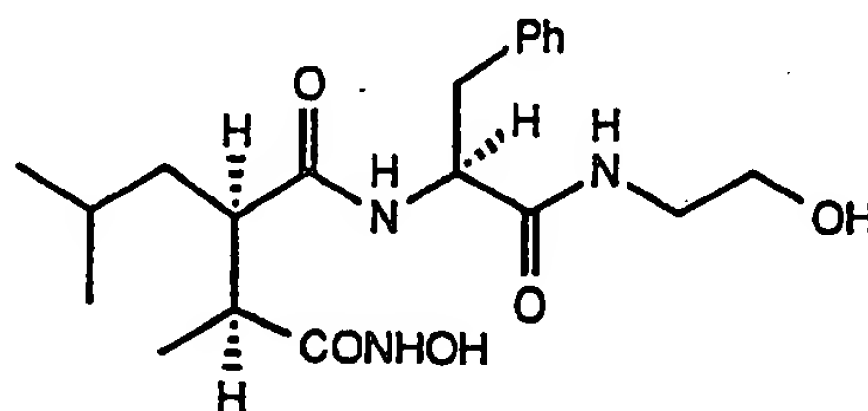
28 Found C 59.30 H 7.91 N 9.94

29

30 Example 15

31

32 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
33 L-phenylalanine-N-(2-hydroxyethyl) amide.



Using the procedure described in Example 13f [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-phenylalanine (0.4g, 0.91mmol) was coupled with ethanolamine (61mg, 1.00mmol) then the product hydrogenated to give the title compound (51mg, 0.13 mmol, 14%)

m.p. 208 - 210°C

$[\alpha]_D = 24.0^\circ$ (c=0.30, MeOH)

$\nu_{\max}(\text{KBr})$ 3280, 2960, 1635, 1540, 1450, and 1370 cm^{-1}

δ_H (250MHz, D_6 -DMSO) 0.39 (3H, d, J= 6Hz, CHCH_3), 0.73 (3H, d, J= 6Hz, $\text{CH}(\text{CH}_3)_2$), 0.80 (3H, d, J= 6Hz, $\text{CH}(\text{CH}_3)_2$), 1.33 (2H, t, J= 10 Hz), 1.94 (1H, t, J= 8Hz), 2.34 (1H, t, J= 10 Hz), 2.77 (2H, t, J= 12 Hz), 3.01 (2H, dd, J= 11,3 Hz), 3.13 (2H, q, J= 6Hz), 4.61 (1H, m), 4.66 (1H, m), 7.20 (5H, m), 7.73 (1H, s), 8.18 (1H, d, J= 8Hz, NH), and 8.69 (1H, s).

δ_C (62.9MHz, D_6 -DMSO) 173.5, 171.4, 138.3, 128.1, 126.3, 59.9, 54.2, 46.8, 41.6, 37.4, 25.4, 24.3, 21.7, and 16.1.

Analysis calculated for $\text{C}_{20}\text{H}_{31}\text{N}_3\text{O}_5 \cdot 0.5\text{H}_2\text{O}$.

1 Required C 59.68 H 8.01 N 10.44

2 Found C 59.38 H 7.71 N 10.27

3

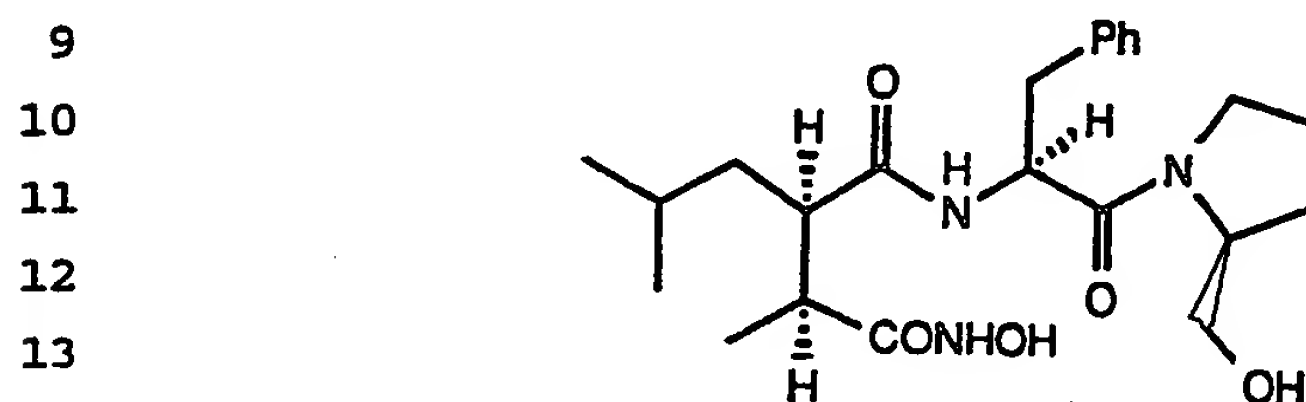
4 Example 16

5

6 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
7 phenylalaninyl-D-prolinol.

8

9



16 Using the procedure described in example 13f
17 [4-(N-Benzoyloxyamino)-2R-isobutyl-3-methylsuccinyl]-
18 L-phenylalanine (0.41g, 1.00mmol) was coupled with
19 S-pyrrolidine methanol (130mg, 1.29mmol) then the
20 product hydrogenated to give the title compound (180mg,
0.41 mmol, 41%)

21

22 $\nu_{\max}(\text{KBr})$ 3310, 2900, 1630, 1540, and 1440 cm^{-1}

23

24 δ_{H} (250MHz, D_6 -DMSO) 0.58 (3H, d, $J=7\text{Hz}$, CH_3CH), 0.78
25 (6H, 2xd, $J=7\text{Hz}$, $\text{CH}(\text{CH}_3)_2$), 0.82 (1H, m, CHMe_2), 1.38
26 (2H, m, CHCH_2CH), 1.82 (4H, m, CH_2CH_2), 2.02 (1H, m,
27 CHCONH), 2.44 (1H, m, CHCONHOH), 3.00 (4H, m, $\text{CH}_2\text{Ph} +$
28 CONHCH_2) 3.42 (1H, m, CONH), 3.62 (3H m, CHCH_2Ph
29 + CH_2OH), 4.70 (1H, m, NHCHCO), and 7.20 (5H, m, Ph).

30

31

32

33

1 Example 17

2

3 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
 4 L-phenylalanine-N-(3-(2-pyrrolidone)propyl) amide
 5 sodium salt.

6

7

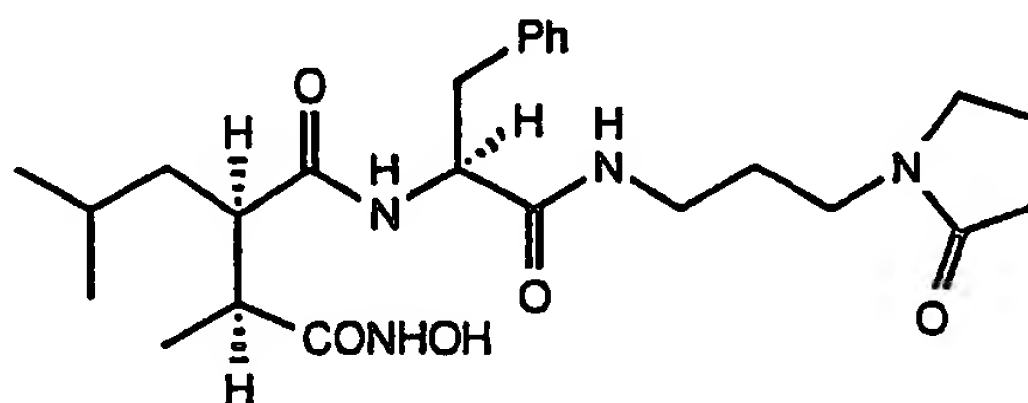
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9

10

11

12



13 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
 14 L-phenylalanine-N-(3-(1-pyrrolidone)propyl) amide
 15 (50mg, 0.1mmol) was dissolved in methanol (1ml) and
 16 sodium hydroxide solution (1.0M, 2.0ml) added to give
 17 a homogeneous solution. The methanol was removed under
 18 reduced pressure then the residual aqueous solution
 19 freeze dried to give the title compound (53mg, 0.1mmol,
 20 100%).

21

22 δ_H (250MHz, D_6 -DMSO) 0.44 (3H, d, $J=7$ Hz, $CHCH_3$), 0.72
 23 (3H, d, $J=6$ Hz, $CH(CH_3)_2$), 0.79 (3H, d, $J=6$ Hz,
 24 $CH(CH_3)_2$), 1.32 (2H, m), 1.53 (2H, q, $J=7$ Hz), 1.92
 25 (4H, m), 2.21 (2H, t, $J=8$ Hz), 2.37 (1H, m), 2.79 (1H,
 26 m), 2.93 (1H, d, $J=5$ Hz), 3.01 (2H, m), 3.13 (2H, t,
 27 $J=7$ Hz), 3.26 - 3.43 (6H, m), 4.54 (1H, m), 7.22 (5H,
 28 m), 7.85 (1H, t, $J=7$ Hz), and 8.28 (1H, d, $J=8$ Hz,
 29 NH).

30

31 δ_C (62.9MHz, D_6 -DMSO) 174.0, 173.4, 170.8, 129.2,
 32 127.7, 126.0, 54.6, 47.0, 46.7, 37.7, 36.3, 30.7,
 33 27.3, 25.4, 24.3, 21.5, 17.7 and 16.1.

1
2 Example 18

3
4 Collagenase inhibition activity

5
6 The potency of compounds of general formula I to act
7 as inhibitors of collagenase (a metalloprotease
8 involved in tissue degradation) was determined by the
9 procedure of Cawston and Barrett, (Anal. Biochem., 99,
10 340-345, 1979), hereby incorporated by reference,
11 whereby a 1mM solution of the inhibitor being tested or
12 dilutions thereof was incubated at 37° for 16 hours
13 with collagen and collagenase (buffered with 25mM
14 Hepes, pH 7.5 containing 5mM CaCl₂, 0.05% Brij 35 and
15 0.02% NaN₃). The collagen was acetylated ¹⁴C collagen
16 prepared by the method of Cawston and Murphy (Methods
17 in Enzymology, 80, 711, 1981), hereby incorporated by
18 reference. The samples were centrifuged to sediment
19 undigested collagen and an aliquot of the radioactive
20 supernatant removed for assay on a scintillation
21 counter as a measure of hydrolysis. The collagenase
22 activity in the presence of 1 mM inhibitor, or a
23 dilution thereof, was compared to activity in a control
24 devoid of inhibitor and the results reported below as
25 that inhibitor concentration effecting 50% inhibition
26 of the collagenase (IC₅₀).

27

<u>Compound of Example No.</u>	<u>IC₅₀</u>
3	200 nM
7	20 nM
9	90 nM

31

32 Examples of unit dosage compositions are as follows:
33

1

2 Example 19

3

4 **Capsules:**

5

6

7

8

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10

11

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13

14

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22

23

24

25

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27

28

29

30

31

32

33

Per 10,000

IngredientsPer CapsuleCapsules

1. Active ingredient

(Cpd of Formula I) 40.0 mg

400 g

2. Lactose 150.0 mg

1500 g

3. Magnesium

stearate 4.0 mg40 g

194.0 mg

1940 g

Procedure for capsules:

Step 1. Blend ingredients No. 1 and No. 2 in a suitable blender.

Step 2. Pass blend from Step 1 through a No. 30 mesh (0.59 mm) screen.

Step 3. Place screened blend from Step 2 in a suitable blender with ingredient No. 3 and blend until the mixture is lubricated.

Step 4. Fill into No. 1 hard gelatin capsule shells on a capsule machine.

1 Example 20

2

3 **Tablets:**

4			Per 10,000
5		<u>Ingredients</u>	<u>Per Tablet</u>
6			<u>Tablets</u>
7	1.	Active ingredient	
8		(Cpd of Form. I)	40.0 mg
9	2.	Corn Starch	20.0 mg
10	3.	Alginic acid	20.0 mg
11	4.	Sodium alginate	20.0 mg
12	5.	Magnesium	
13		stearate	<u>1.3 mg</u>
14			<u>13 g</u>
			101.3 mg
			1013 g

17 Procedure for tablets:

18 Step 1. Blend ingredients No. 1, No. 2, No. 3 and No.
19 4 in a suitable mixer/blender.

20 Step 2. Add sufficient water portionwise to the blend
21 from Step 1 with careful mixing after each
22 addition. Such additions of water and mixing
23 until the mass is of a consistency to permit
24 its conversion to wet granules.

25 Step 3. The wet mass is converted to granules by
26 passing it through an oscillating granulator
27 using a No. 8 mesh (2.38mm) screen.

28 Step 4. The wet granules are then dried in an oven at
29 140°F (60°C) until dry.

30 Step 5. The dry granules are lubricated with
31 ingredient No. 5.

32 Step 6. The lubricated granules are compressed on a
33 suitable tablet press.

1

2 Example 21

3

4 **Intramuscular Injection:**

5	<u>Ingredient</u>	<u>Per ml.</u>	<u>Per liter</u>
6	1. Formula I compound		
7	Active ingredient	10.0 mg	10 g
8	2. Istonic buffer		
9	solution pH 4.0.	q.s.	q.s.

10

11 **Procedure:**

12 Step 1. Dissolve the active ingredient in the buffer
13 solution.

14 Step 2. Aseptically filter the solution from Step 1.

15 Step 3. The sterile solution is now aseptically
16 filled into sterile ampoules.

17 Step 4. The ampoules are sealed under asptic
18 conditions.

19

20 Example 22

21

22 **Suppositories:**

23			Per
24	<u>Ingredients</u>	<u>Per Supp.</u>	<u>1,000 Supp</u>
25	1. Formula I compound		
26	Active ingredient	40.0 mg	40 g
27	2. Polyethylene Glycol		
28	1000	1350.0 mg	1,350 g
29	3. Polyethylene Glycol		
30	4000	<u>450.0 mg</u>	<u>450 g</u>
31		1840.0 mg	1,840 g

32 **Procedure:**

33 Step 1. Melt ingredient No. 2 and No. 3 together and

- 1 stir until uniform.
- 2 Step 2. Dissolve ingredient No. 1 in the molten mass
- 3 from Step 1 and stir until uniform.
- 4 Step 3. Pour the molten mass from Step 2 into
- 5 suppository moulds and chill.
- 6 Step 4. Remove the suppositories from moulds and
- 7 wrap.
- 8

9 Example 23

10

11 Eye Ointment

12

13 An appropriate amount of a compound of general formula

14 I is formulated into an eye ointment base having the

15 following composition:

16

17	Liquid paraffin	10%
18	Wool fat	10%
19	Yellow soft paraffin	80%

20

21 Example 24

22

23 Topical skin ointment

24

25 An appropriate amount of a compound of general formula

26 I is formulated into a topical skin ointment base

27 having the following composition:

28

29	Emulsifying wax	30%
30	White soft paraffin	50%
31	Liquid paraffin	20%

32

33

1 CLAIMS

2

3 1. A compound of general formula I:

4

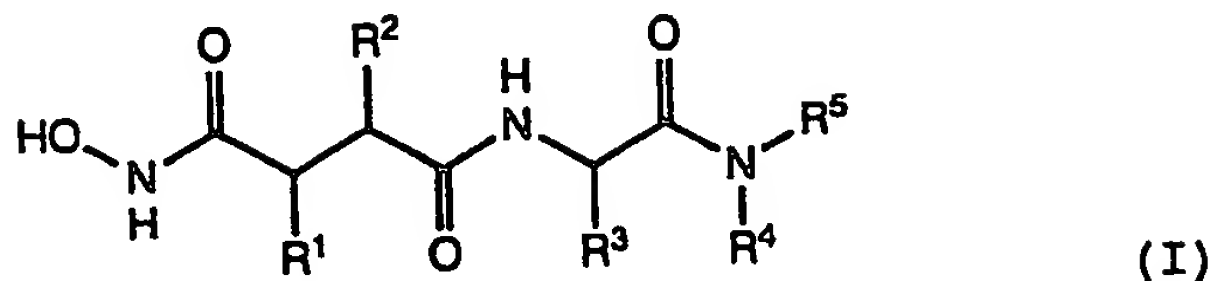
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10

11

12 wherein:

13

14 R^1 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6
 15 alkenyl, phenyl, phenyl(C_1-C_6)alkyl, C_1-C_6
 16 alkylthiomethyl, phenylthiomethyl, substituted
 17 phenylthiomethyl, phenyl(C_1-C_6)alkylthiomethyl or
 18 heterocyclylthiomethyl group; or R^1 represents
 19 $-S-R^X$ wherein R^X represents a group

20

21

22

23

24

25

26 R^2 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6
 27 alkenyl, phenyl(C_1-C_6)alkyl, cycloalkyl(C_1-C_6)-
 28 alkyl, or cycloalkenyl(C_1-C_6)alkyl;

29

30 R^3 represents an amino acid side chain or a C_1-C_6
 31 alkyl, benzyl, (C_1-C_6)alkoxybenzyl, benzyloxy-
 32 (C_1-C_6)alkyl or benzyloxybenzyl group;

33

1 R^4 represents a hydrogen atom or a methyl group;

2

3 R^5 represents a group $(CH_2)_nA$;

4

5 or R^4 and R^5 together represent a group

6

7

8

9

10 Q represents CH_2 or CO;

11

12 m is an integer from 1 to 3;

13

14 n is an integer from 1 to 6; and

15

16 A represents a hydroxy, (C_1-C_6) alkoxy,
17 (C_2-C_7) acyloxy, (C_1-C_6) alkylthio, phenylthio,
18 (C_2-C_7) acylamino or N-pyrrolidone group

19

20 or a salt and/or N-oxide and/or (where the compound is
21 a thio-compound) a sulphoxide or sulphone thereof.

22

23 2. A compound as claimed in claim 1, in which the
24 chiral centre adjacent the substituent R^3 has S
25 stereochemistry.

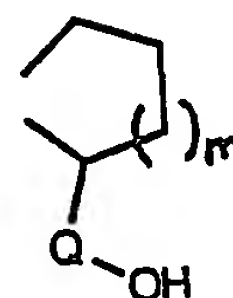
26

27 3. A compound as claimed in Claim 1 or 2, wherein R^1
28 represents a hydrogen atom or a C_1-C_4 alkyl,
29 phenylthiomethyl or heterocyclylthiomethyl group.

30

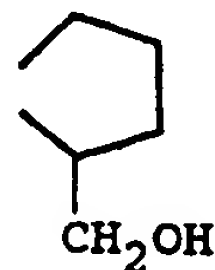
31 4. A compound as claimed in Claim 1, 2 or 3, wherein
32 R^2 represents a C_3-C_6 alkyl group.

33



1 5. A compound as claimed in any one of Claims 1 to 4,
2 wherein R^3 represents a benzyl,
3 4-(C₁-C₆)alkoxyphenylmethyl or benzyloxy benzyl group.
4

5 6. A compound as claimed in any one of Claims 1 to 5,
6 wherein R^4 represents a hydrogen atom or R^4 and R^5
7 together represent a group
8



12 7. A compound as claimed in any one of Claims 1 to 6,
13 wherein n has the value 1, 2 or 3.
14

15 8. A compound as claimed in any one of Claims 1 to 7,
16 wherein R^5 represents a pyrrolidone, hydroxy, methoxy
17 or thioethyl group.
18

19 9. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
20 phenylalanine-N-(2-hydroxyethyl)-amide;
21

22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
23 phenylalaninyl-proline;
24

25 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
26 phenylalanine-N-(2-hydroxyethyl)-N-methylamide;
27

28 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
29 phenylalaninyl-D-prolinol;
30

31 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
32 phenylalaninyl-L-prolinol;
33

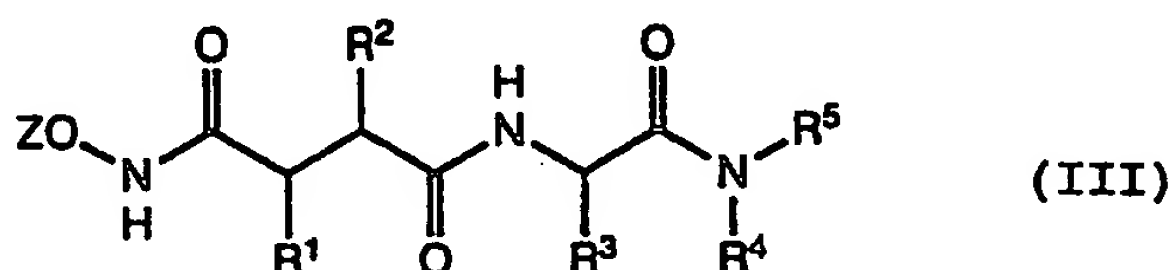
- 1
- 2 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 3 phenylalanine-N-(5-N-methyl-pentylcarboxamide)
- 4 amide;
- 5
- 6 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 7 phenylalanine-N-(2-ethyl thioethyl) amide;
- 8
- 9 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 10 phenylalanine-N-(2-methoxyethyl) amide;
- 11
- 12 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 13 phenylalanine-N-(2-N-acetyethyl) amide;
- 14
- 15 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 16 phenylalanine-N-(3-(2-pyrrolidone)propyl) amide;
- 17
- 18 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 19 phenylalanine-N-(3-(2-pyrrolidone)propyl) amide
- 20 sodium salt;
- 21
- 22 [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-
- 23 phenylalanine-N-(2-acetoxyethyl) amide;
- 24
- 25 [4-(N-Hydroxyamino)-2R-isobutyl-3S-
- 26 methylsuccinyl]-L-phenylalanine-N-(3-(2-
- 27 pyrrolidone)propyl) amide;
- 28
- 29 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
- 30 succinyl]-L-phenylalanine-N-methyl-N-(2-hydroxy-
- 31 ethyl) amide;
- 32
- 33

- 1 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
2 succinyl]-L-phenylalanine-N-(2-hydroxyethyl)
3 amide;
4
- 5 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
6 succinyl]-L-phenylalaninyl-D-prolinol; or
7
- 8 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-
9 succinyl]-L-phenylalanine-N-(3-(2-pyrrolidone)pro-
10 pyl) amide sodium salt;
11
- 12 or a free base, free acid or salt thereof.
13
- 14 10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
15 L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide or
16
- 17 [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-L-
18 phenylalanine-N-(3-(2-pyrrolidone)propyl)amide,
19
- 20 or a salt thereof.
21
- 22 11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-methylsuccinyl]-
23 L-phenylalanine-N-(3-(2-pyrrolidone)propyl)amide or a
24 salt thereof.
25
- 26 12. A compound as claimed in any one of claims 1 to 11
27 for use in human or veterinary medicine.
28
- 29 13. The use of a compound as claimed in any one of
30 claims 1 to 11 in the preparation of an agent for use
31 in the management of disease involving tissue
32 degradation and/or in the promotion of wound healing.
33

1 14. A pharmaceutical or veterinary formulation
2 comprising a compound as claimed in any one of claims 1
3 to 11 and a pharmaceutically and/or veterinarily
4 acceptable carrier.

5
6 15. A process for preparing a compound of general
7 formula I as defined in claim 1, the process
8 comprising:

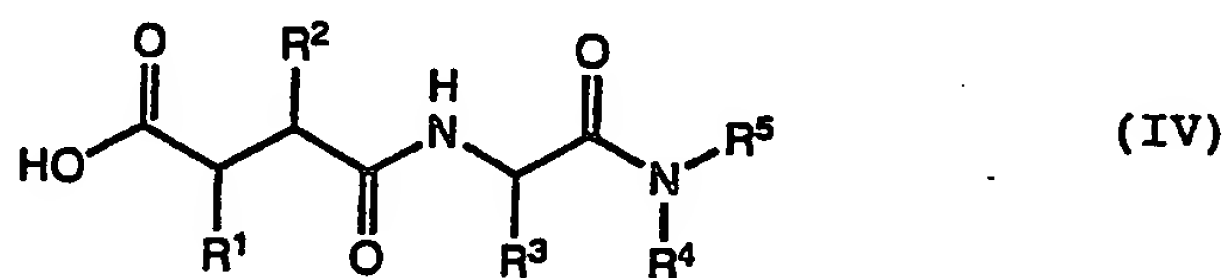
9
10 (a) deprotecting a compound of general formula III



16 wherein:

17
18 R^1 , R^2 , R^3 , R^4 and R^5 are as defined in general
19 formula I and Z represents a protective group; or

20
21 (b) reacting a compound of general formula IV



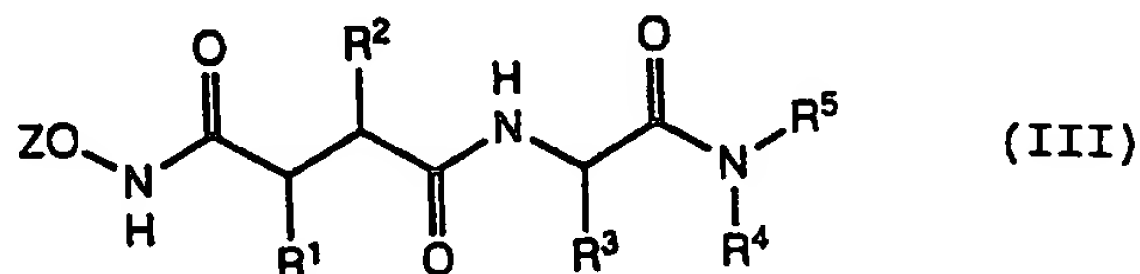
27 wherein:

28
29 R^1 , R^2 , R^3 , R^4 and R^5 are as defined in general
30 formula I, with the proviso that R^1 represents a
31 hydrogen atom,

32
33 with hydroxylamine or a salt thereof; and

(c) optionally after step (a) or step (b) converting a compound of general formula I into another compound of general formula I.

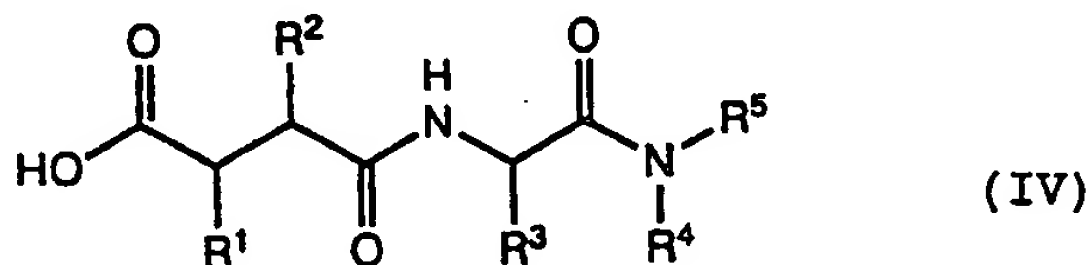
16. A compound of general formula III



wherein:

R¹, R², R³, R⁴ and R⁵ are as defined in general formula I and Z represents a protective group.

17. A compound of general formula IV



wherein:

R¹, R², R³, R⁴ and R⁵ are as defined in general formula I, with the proviso that R¹ represents a hydrogen atom.

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